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I, NEIL H. HUGHES, a Notary Public, in and for the Province of Ontario, by Royal Authority duly appointed, residing in the City of Mississauga, in the Regional Municipality of Peel in said Province, DO CERTIFY AND ATTEST that the paper-writing hereto annexed is a true copy of a document produced and shown to me and purporting to be Declaration of Michael Mantle Lipp Ph.D., the said copy having been compared by me with the said original document, an act whereof being requested I have granted under my Notarial Form and Seal of Office to serve and avail as occasion shall or may require.

IN TESTIMONY WHEREOF I have hereto subscribed my name and affixed my Notarial Seal of Office at the Town of Markham, in the Regional Municipality of York, this 13th day of November, 2003.

A Notary Public in and for the Province of Ontario

NEIL HARVEY HUGHES, Notary Public, Province of Ontario, limited to the attestation of instruments and the taking of affidavits, for Ivor M. Hughes, Barrister and Solicitor, Patent & Trademark Agents. Expires March 30, 2004.

IN THE MATTER OF THE UNITED STATES PATENT APPLICATION SERIAL **NO. 09/719,142,** IN FAVOUR OF **BERNARD CHARLES SHERMAN,** APPLICANT AND THE INVENTOR OF THE SUBJECT MATTER THEREIN, FILED December 8, 2000.

DECLARATION

I, **Michael Mantle Lipp Ph.D.**, Staff Scientist of Alkermes Inc. SOLEMNLY DECLARE AND AFFIRM THE FOLLOWING:

1. I am currently employed at Alkermes Inc. (a pharmaceutical and drug delivery technology company located in Cambridge, Massachusetts) in the position of Staff Scientist. Presently, I am a senior member of the Pulmonary Formulations Division and work in the areas of preformulation, formulation and solid-state analysis of pharmaceutical compositions for various routes of administration, including pulmonary and oral. I hold a Ph.D. in Chemical Engineering from the University of California. A copy of my curriculum vitae is attached as Exhibit A to this my Declaration. As such I believe I am well qualified to comment and provide opinion in these matters

2. The following paragraphs contain my comments and opinions concerning the United States Patent Office Examiner's Final Action dated December 18, 2002 (hereafter referred to as the Final Action) concerning U.S. Patent Application No. 09/719,142 entitled "Pharmaceutical Tablets Comprising An NSAID And A Prostaglandin" (hereafter referred to as the '142 patent application).

3. I was asked by Neil H. Hughes, Patent Agent of the firm Ivor M. Hughes, Barristers and Solicitors, Patent and Trade Mark Agents and Counsel for the inventor Dr. Bernard Charles Sherman, to provide my opinion concerning the position taken by the United States Patent Office Examiner in the Final Action and his rejection of claims 1 through 11 of the '142 patent application. In particular, I was asked to provide my opinion with respect to the Examiner's allegation that pending claims 1 through 11 set

out in the '142 patent application are unpatentable over Sims et al. (U.S. Patent No. 5,288,507) in view of Stuerzebecher et al. (U.S. Patent No. 5,523,321) and Kararli et al. (U.S. Patent No. 5,935,939) and also unpatentable over Franz et al. (U.S. Patent No. 5,232,704) in view of Stuerzebecher (U.S. Patent No. 5,523,321).

4. In my opinion, the inventions described in claims 1 through 11 set out in the '142 patent application are **not** obvious in light of the teachings and disclosures of U.S. Patent No. 5,288,507 (hereafter referred to as the '507 patent) in view of U.S. Patent No. 5,523,321 (hereafter referred to as the '321 patent) and U.S. Patent No. 5,935,939 (hereafter referred to as the '939 patent) and also are **not** obvious in light of the teachings and disclosures of U.S. Patent No. 5,232,704 (hereafter referred to as the '704 patent) in view of the '321 patent. I thus disagree with the conclusions reached by the Examiner the Final Action with respect to the '142 patent application. I describe my opinions further below, beginning with a summary of the claimed inventions in question of the '142 patent application followed by my opinion with respect to the Examiner's comments and conclusions concerning the teachings and claimed inventions of the '507, '329, '939 and '704 patents.

Summary of the Inventions of the '142 Patent Application

5. The '142 patent application discloses a novel combination tablet formulation for the co-administration of a non-steroidal anti-inflammatory drug (NSAID) and a prostaglandin, in particular misoprostol, that possesses several advantages over other related formulations disclosed in the art with respect to drug stability and formulation ease of manufacture, among others. As described in the '142 patent application, the co-administration of the prostaglandin misoprostol with NSAIDs is known to be useful for the treatment and prevention of NSAID-induced ulcers, a known side effect associated with chronic administration of NSAIDs.

6. As also described in the '142 patent application, the primary motivation for the development of the novel disclosed combination NSAID:misoprostol tablet formulation

was to address stability problems known to be associated with misoprostol in pharmaceutical formulations in general and incompatibility issues between misoprostol and NSAIDs in particular. For example, it is stated on pages 1 and 2 of the '142 patent application that:

> *"It is desirable to provide a pharmaceutical composition which exhibits the beneficial properties of an NSAID and which also exhibits the beneficial properties of misoprostol for countering the ulcerogenic side effects attendant to NSAID administration.*
>
> *This can be achieved by combining an NSAID and misoprostol in a single pharmaceutical tablet. However this is not easy to do, because misoprostol is highly unstable, and it is thus desirable not to have the misoprostol and NSAID mixed together, so as to prevent any deleterious effect of the NSAID on the stability of the misoprostol."*

7. The solution to these issues related to misoprostol chemical stability captured in the inventions of the '142 patent application involves the development of a novel combination tablet formulation that serves to protect and isolate the misoprostol incorporated therein from both the NSAID and the tablet surface. This novel combination tablet formulation is comprised of individual, pharmaceutically acceptable tablets (two total) containing the NSAID (tablet 1) and misoprostol (tablet 2, with both tablets containing additional excipients as standardly included in tablet formulations) embedded in a single larger combination tablet via compression in the presence of an additional excipient or mixture of excipients which serves to form a shell around the individual single-drug tablets. This excipient shell serves both to separate the embedded NSAID tablet from the embedded misoprostol tablet and to prevent exposure of the misoprostol tablet to the surface of the combination tablet. As a result, the probability of the occurrence of deleterious chemical reactions between misoprostol and the NSAID or between misoprostol and water or oxygen at the tablet surface is greatly reduced.

8. In my opinion, it is also important to note with respect to the matter at hand that the novel combination tablet formulation disclosed in the '142 patent application contains two individual tablets containing the NSAID (tablet 1) and misoprostol (tablet 2) that are themselves pharmaceutically acceptable tablets that could be administered as such separately. For example, Example 1 of the '142 patent application describes the production of a tablet weighing 80 mg containing 50 mg of diclofenac sodium in addition to microcrystalline cellulose, croscarmellose sodium and magnesium stearate (optionally with an enteric coating added to the tablet shell). Example 2 of the '142 patent application describes the production of a tablet weighing 30 mg containing 200 μg of misoprostol in addition to hydroxypropylmethylcellulose, microcrystalline cellulose, magnesium stearate and croscarmellose sodium. As I will discuss further below, although these tablets are small in size with respect to typical pharmaceutical tablets, they are still within a size range and produced in a manner that is consistent with the conventional definition of a pharmaceutical tablet. As I will also discuss further below, the use of two smaller pharmaceutically acceptable tablets, one containing misoprostol and the other containing the NSAID, provides advantages with respect to both chemical stability and ease of manufacture and processability and was not taught towards or disclosed in any of the additional references that I was provided with related to this matter.

9. The inventions of the '142 patent application are essentially summarized and captured in Claims 1 and 2 of the application. For example, Claim 1 states:

> *"Claim 1 (previously amended): A pharmaceutical tablet comprising a shell in which is imbedded two smaller tablets covered by the material of the shell of the pharmaceutical tablet, one of which smaller tablets comprises an NSAID and the other of which smaller tablets comprises misoprostol, whereby the two smaller tablets are not exposed to the environment at the surface of the pharmaceutical tablet, being protected by said shell."*

Similarly, Claim 2 states:

"Claim 2 (original): The pharmaceutical tablet of Claim 1 wherein the smaller tablet containing the NSAID is enteric coated."

10. With respect to the advantages of the novel disclosed tablet formulation as compared to existing misoprostol:NSAID combination formulations described in the art, the inventor of the '142 patent application refers to a previously disclosed tablet formulation containing a NSAID and misoprostol. This combination NSAID:misoprostol tablet formulation is disclosed in U.S. Patent No. 5,601,843 (Gimet et al., hereafter referred to as the '843 patent and included as Exhibit B to this my Declaration). The '843 patent discloses core/mantle tablet formulations comprised of a core of NSAID surrounded by a mantle of misoprostol, optionally with additional coating layers (including an enteric coating layer) located in between the core and mantle layers.

11. The '843 patent describes three embodiments of the disclosed core/mantle tablets, these being (1) a NSAID core simply surrounded by a mantle containing misoprostol, (2) a NSAID core covered by an enteric coating layer surrounded by a mantle containing misoprostol and (3) a NSAID core covered by an intermediate coating layer of HPMC (the undercoat as described in the '843 patent), an enteric coating layer and an additional intermediate coating layer covering the enteric coating layer (the overcoat as described in the '843 patent) surrounded by a mantle of misoprostol. For example, with respect to embodiment (3), it is stated in the '843 patent that (column 6, line 45 through column 7, line 10):

"A third embodiment of the composition is shown in FIG. 3. In FIG. 3, a tablet 24 is illustrated in cross section. The tablet 24 consists of an inner core 26 comprising an NSAID or its salt as disclosed with regard to the core 12 of FIG. 1. Surrounding the core 26 is an undercoat 28 which can provide a surface for the enteric coat which undercoat can have a greater affinity for the enteric coat than the core alone. The coating 28 can be any suitable coating material and preferably is HPMC in an amount about two percent (2%) by weight of the core.

An aqueous enteric coating 30 can be used to segregate the NSAID from the prostaglandin and to aid in controlling release of the NSAID. The undercoat 28 prevents water which can be present in the aqueous enteric coat 30 from penetrating into the NSAID core to cause any undesirable effects on the NSAID which might be caused by water. The enteric coating 30 can aid in the prevention of degradation of the prostaglandin by the presence of the NSAID as well as direct delivery of the NSAID in the lower G.I. tract rather than the stomach. Any aqueous enteric coating can be used and the enteric coating can be coated onto the inner core using standard coating techniques as described with regard to the embodiment shown in FIG. 2.

An overcoat 32 is coated over the enteric coat 30. The overcoat 32 can provide an intermediate coating providing affinity between the enteric coat and mantle. The overcoat can be any suitable material, preferably the overcoat is HPMC in an amount about three percent (3%) by weight of the core. The overcoat 32 prevents water which can be present in the aqueous enteric coating from passing into the prostaglandin mantle. Further, the overcoat can aid in maintaining the integrity of the enteric coating during the compression coating step as the mantle is formed on the tablet."

12. In my opinion, embodiment (3) is most relevant with respect to comparison with the combination tablet formulations disclosed in the '142 patent, since this embodiment is the only one for which the misoprostol mantle is adequately protected from contact with the NSAID core and also protected from exposure to residual water contained in the intermediate enteric coating layer. For embodiment (1), the mantle containing misoprostol is in direct contact with the core containing the NSAID, which is suboptimal in light of the known stability and incompatibility issues between misoprostol and NSAIDS discussed above. For embodiment (2), the presence of water in the enteric coating layer could also act to degrade misoprostol due to the extensive contact area between the enteric coating layer covering the core and the misoprostol in the mantle. Thus, embodiment (3) is the only embodiment disclosed in the '843 patent that potentially adequately addresses the concern of separating the NSAID and misoprostol

containing phases from coming into direct contact and of ensuring for stability of misoprostol at the interface between these phases; embodiments (1) and (2) are clearly suboptimal and inferior to the novel combination tablet formulations disclosed in the '142 patent application.

13. However, as discussed in the '142 patent application, embodiment (3) of the '843 patent possesses the disadvantage of requiring multiple coating layers between the NSAID core and the misoprostol mantle layer (as I will discuss below, this disadvantage is also particularly important with respect to a consideration of the cost and complexity of the manufacturing processes required to produce such a multi-layered dosage formulation). Additionally, as also discussed in the '142 patent application, embodiment (3) still does not address the exposure of misoprostol at the surface of the tablet. Given the known poor stability of misoprostol, this exposure of misoprostol at the tablet surface is still suboptimal with respect to chemical stability of misoprostol. The surfaces of solid pharmaceutical dosage formulations are known to be environments for which destabilizing chemical reactions can occur due to the presence of light, oxygen and adsorbed water. For example, it is stated on page 2 of the '142 patent that:

> *"While the invention of US Patent 5601843 accomplishes its objective of separating the NSAID from the misoprostol, it has certain disadvantages. One disadvantage is the need to have a coating on the inner core in order to completely prevent contact between the NSAID in the inner core and the misoprostol in the mantle.*
>
> *A second disadvantage is that the misoprostol is dispersed throughout the mantle, and is thus exposed to the environment at the surface of the tablet. This exposure increases the vulnerability of the misoprostol to degradation due to the effects of light or atmospheric oxygen and moisture.*

The object of the present invention is to enable a pharmaceutical tablet that incorporates both an NSAID and misoprostol, but overcomes these disadvantages."

14. Thus, I agree with the inventor of the '142 patent application with respect to the statement that the combination formulations disclosed in the '142 patent application possess advantages over the combination formulations disclosed in the '843 patent, namely that the compositions disclosed in the '142 patent application (i) do not require the presence of a core containing NSAID coated with one or more layers to prevent the contact of NSAID with misoprostol and (ii) provide for the protection of the misoprostol containing smaller tablet from exposure to the surface of the combination tablet.

15. Additionally, in my opinion, the inventions of the '142 patent application possess several additional and important advantages and novelties over the prior art disclosures both described in the '142 patent application (i.e., the '843 patent) and cited by the Examiner as described below. As I discussed above, the '142 patent application focuses on providing a solution for known instability and incompatibility issues associated with the inclusion of misoprostol into pharmaceutical dosage forms such as tablets, in particular in combination tablet formulations with NSAIDs. As I also discussed above, the solution disclosed in the '142 patent application provides for the stabilization of misoprostol via both minimizing and preventing the contact between misoprostol and the NSAID in the combination tablet and preventing exposure of misoprostol at the surface of the tablet. In my opinion, the solution identified in the '142 patent is ingenious and unexpected with respect to its efficacy in addressing the stability issues related to the presence of misoprostol as well as its simplicity with respect to ease of manufacturability. For example, with respect to the manufacturing process described in the '142 patent for the production of the disclosed combination tablets, it is stated on pages 3 and 4 of the '142 patent application that:

"Compositions (i.e. tablets) of the present invention may be made as follows:

1. *Firstly, a tablet comprising the NSAID and a tablet comprising the misoprostol are made in separate tabletting operations. The portion of the composition which surrounds the two smaller tablets will be referred to herein as the "shell".*

2. *Then the final composition is assembled in a further tabletting operation as follows:*

   (i) *Part of the powder or granular mix of which the shell is to be comprised is filled into the die, into which a punch has been inserted from below.*

   (ii) *One of the smaller tablets comprising the NSAID and one of the smaller tablets comprising the misoprostol are then inserted into the die.*

   (iii) *The balance of the powder or granular mix of which the shell is to be comprised is then filled into the die to cover two smaller tablets.*

   (iv) *The upper punch is then inserted into the die from above and pressure is applied between the punches to compress the powder or granular mix around the two smaller tablets into the form of the final tablet.*

   (v) *The upper punch is then withdrawn and the lower punch is raised further into the die to eject the composition."*

16. In my opinion, a key aspect of the process detailed above is the fact that a smaller yet pharmaceutically acceptable tablet containing misoprostol alone in combination with conventional tablet excipients (i.e., without the NSAID) is produced separately and then combined with a smaller tablet containing the NSAID in a simple one-step process of

compression in the dry state in a tablet press with a shell of surrounding excipient. As a result, smaller stable tablets containing misoprostol can initially be produced in a manner which optimizes the stability of misoprostol (i.e., by a simple dry direct compression process for example, in light of the fact that misoprostol is known to be stable in the presence of water as I will describe below) without the concern of the misoprostol coming into contact with the NSAID. The subsequent combining of a smaller tablet containing misoprostol with an additional tablet containing a NSAID in a simple one-step process of compression in the dry state in a tablet press with a shell of surrounding excipient thus (i) does not require the use of any processing steps that require the simultaneous presence of misoprostol, the NSAID and water, such as would occur in a wet granulation processing step, (ii) minimizes the manufacturing time for which misoprostol and the NSAID are both present and (iii) minimizes and prevents virtually all contact between misoprostol-containing and NSAID-containing phases as well as exposure of misoprostol to the combination tablet surface.

17. Thus, in my opinion, by effectively decoupling the processing of formulations containing an NSAID and misoprostol via (1) the formation of two separate small tablets containing the individual drugs and then (2) the combining of these two smaller tablets into a single combination tablet with a protective shell of excipient via simple compression in the dry state in a tablet press as described above, the inventors of the '142 patent circumvent the known instability issues related to misoprostol in the presence of an NSAID without requiring (i) the use of complex manufacturing equipment or costly unit operation steps such as multiple core coating steps, (ii) the formation of granules via wet granulation, (iii) the formation of an amorphous dispersion of misoprostol with excipient, or any other process that would increase the cost or manufacturing complexity of combination tablet production.

18. Additionally, as I will discuss further below with respect to the prior art cited by the Examiner, misoprostol was known to possess poor stability in general and to be unstable in the presence of water in particular. As a result, in my opinion, the use of processes such as wet granulation, spray drying, coating of a mantle of misoprostol and

excipient onto a core containing a NSAID, etc. for the production of dosage forms containing misoprostol, such as the processes described in the prior art cited by the Examiner in the Final Action, would have been avoided for use by a skilled formulator due to their potential to deleteriously affect the stability of misoprostol. A skilled formulator would have known that such process require the direct contact of misoprostol with water or the formation of a fluidized phase containing misoprostol and water or another solvent or excipient, which would cause the misoprostol to be in a more mobile and fluid state than in the solid phase and thus increase the potential for misoprostol to degrade during processing.

19. Thus, for the reasons described above, in my opinion, the combination NSAID:misoprostol tablet formulations disclosed in the '142 patent are novel and unexpected with respect to the state of the art as of the filing date of the '142 patent. As a result, I disagree with the statements made by the Examiner with respect to the obviousness or lack thereof of the inventions of the '142 patent as I describe below.

The Combined Teachings of the '507, '321 and '939 Patents

20. In the Final Action, the Examiner states that claims 1 and 2 of the '142 patent application are obvious in light of and thus unpatentable over Sims et al. (the '507 patent) in view of Stuerzebecher et al. (the '321 patent) and Kararli et al. (the '939 patent). With respect to his interpretation of the combined teachings of these three patents, the Examiner states on pages 2 and 3 of the Final Action that:

> *"Sims teaches compositions comprising a NSAID (ibuprofen)(col. 1, lines 51-53) and misoprostol (col. 4, lines 61-64). The composition may be administered in tablet form (col. 5, lines 1-3). Sims does not teach that NSAID and misoprostol are separately small tablets.*
>
> *Kararli teaches that prostaglandins such as misoprostol are unstable and decompose above room temperature. Stabilized amorphous dispersions of*

prostaglandins should be used in preparing pharmaceutical dosages. Kararli does not teach that NSAID and misoprostol are separately small tablets.

Stuerzebecher teaches the granulation of several components including prostaglandin and an antagonist that is then molded into round tablets. The amounts of prostaglandin and antagonist are greatly reduced in comparison with the necessary dosages of the individual active substances.

It is the examiner's position that whereas Stuerzebecher does not term granules that make up the composition "tablets", granules are tablets of a specific size, and thus makes the use of "tablets" in the instant invention obvious. Motivation to utilize prostaglandin in combination with an NSAID such as ibuprofen would arisen in order to decrease the amount of prostaglandin and NSAID in comparison to taking the drugs separately. Furthermore, motivation to use a prostaglandin that has been dispersed in an excipient as taught by Kararli would have arisen in order to stabilize misoprostol used therein."

21. Thus, the examiner essentially claims the following with respect to the individual and combined teachings of these three patents:

a. Sims et al. (the '507 patent) teaches compositions of NSAIDs and misoprostol in tablet form (the Examiner does note that Sims does not teach a tablet dosage form comprised of two smaller individual tablets containing the NSAID and misoprostol as taught in the '142 patent application).

b. Kararli et al. (the '939 patent) teaches the use of stabilized amorphous dispersions of misoprostol for use in pharmaceutical dosage forms (the Examiner does note that Kararli et al. does not teach a tablet dosage form comprised of two smaller individual tablets containing the NSAID and misoprostol as taught in the '142 patent application).

c. Stuerzebecher et al. (the '321 patent) teaches the granulation of several components that include prostaglandins and antagonists followed by molding into

tablets that allow for the use of greatly reduced amounts of these drug agents compared to amounts typically required for use of the individual drug agents. The Examiner claims that this would have motivated a skilled formulator to follow the teachings of Stuerzebecher et al and utilize a prostaglandin in combination with a NSAID in order to decrease the amounts of prostaglandin and NSAID needed. The Examiner also takes the position that granules are tablets of a specific size, thus rendering the combination of two smaller tablets in the '142 patent application obvious.

22. As I describe below, I disagree with the Examiner's conclusions regarding the combined teachings of the '507, 321 and '939 patents summarized above. In my opinion, these three patents, read alone or in combination, do not render the inventions of the '142 patent obvious. Further, it is also my opinion that these three patents (i) in part teach away from each other and thus should not be read together (ii) do not make obvious the inventions of the '142 patent application and (iii) in fact teach away from the inventions of the '142 patent application. For similar reasons, I would not expect that a skilled formulator would have been motivated to follow the combined teachings of these three patents when trying to develop a stabilized combination tablet formulation containing a NSAID and misoprostol. I first review the pertinent information disclosed in each of these three patents then provide my opinions concerning their combined teachings.

The Disclosures and Teachings of the '507 patent (Sims et al.)

23. The '507 patent, entitled "Ibuprofen Antacid Combinations" (Sims et al., included as Exhibit C to this my Declaration), discloses and claims pharmaceutical compositions for use in the treatment of pain and inflammation as well as various stomach conditions (upset stomach, etc.) comprised of the NSAID (S)-ibuprofen, an antacid and optionally an anti-gas agent. The inventors of the '507 patent claim that the novel features of the inventions disclosed therein primarily involve (1) the use of the (S)-isomer, or active isomer of ibuprofen in lieu of the racemic form and (1) the development of combination formulations containing both (S)-ibuprofen and an antacid.

24. Misoprostol is briefly mentioned in the '507 patent as being one of a wide range of optional pharmaceutical agents that can be included in the combination (S)-ibuprofen:antacid formulations. For example, it is stated in the '507 patent that (column 4, lines 61 through 69):

> *"The composition of the instant invention may further comprise an antiulcerative agent such as sucralfate, misoprostol and the like. The composition of the instant invention may also further comprise an pro-motility agent to improve gastro/esophageal peristalsis and relieve the symptoms of indigestion. Such an pro-motility agent is selected from metoclopramide hydrochloride, cisapride and the like."*

This is the sole reference to misoprostol or any other prostaglandin contained in the '507 patent. It is also important to note in my opinion with respect to this matter that there is no mention nor teachings concerning any instability issues with respect to misoprostol contained in the '507 patent.

25. With respect to the specific nature of the dosage forms disclosed in the '507 patent, the inventors of the '507 patent provide only generic and conventional information concerning a wide range of dosage forms such as tablets, capsules and syrups, among others. For example, it is stated in the '507 patent that (column 5, lines 1 through 3):

> *"The instant composition may be administered in the form of tablets, caplets, gelcaps, capsules, elixirs, syrups or a suspension."*

The above statement is followed by an extensive list of generic excipients that are standardly included in such formulations. Additionally, four examples of pharmaceutical tablet compositions are provided in the '507 patent (I have made the assumption that the sustained release formulations included as Examples 3 and 4 are tablets although the '507

patent does not specify if this is indeed the case); none of these either list misoprostol or a NSAID other than (S)-ibuprofen as being contained in the formulation or describe a tablet composition comprised of two smaller tablets embedded in a shell of excipient. In fact, no information is provided at all in these examples concerning the processes or procedures by which the tablets are made.

The Disclosures and Teachings of the '321 patent (Stuerzebecher et al.)

26. The '321 patent entitled "Prostacyclins, Their Analogs or Prostaglandins and Thromboxane Antagonists for Treatment of Thrombotic and Thromboembolic Syndromes" (Stuerzebecher et al., included as Exhibit D to this my Declaration) discloses combination formulations containing either a prostaglandin, prostacyclin or analog thereof and a thromboxane receptor antagonist for the treatment of thrombotic and thromboembolic syndromes and diseases. As stated in the '321 patent, the syndromes focused on in the '321 patent include elevated platelet aggregation and clotting, coronary heart diseases and other related cardiovascular system diseases. A range of other diseases and syndromes are also listed in the '321 patent (column 1) that include inhibition of gastric acid secretion and cytoprotection of the gastrointestinal mucous membranes; however, as I mentioned above, these do not appear to be related to the focus of the inventions and are not discussed further to any extent in the '321 patent.

27. The inventors of the '321 patent also state that additional pharmaceutical agents can be included in the disclosed combination formulations, including anticoagulants such as aspirin, among others. Notably, the inventors of the '321 patent do not list nor describe with respect to any of the disclosed formulations either (1) the inclusion in any of the disclosed formulations of any drugs specifically acting as analgesic or anti-inflammatory agents or (2) the inclusion of any NSAIDs in any of the disclosed formulations. As I will also discuss further below, misoprostol is not listed as being a prostaglandin suitable for inclusion in the formulations disclosed and taught in the '321 patent and does not appear to be suitable in general for inclusion in the formulations

disclosed in the '321 patent for the treatment purposes described by the inventors of the '321 patent.

28. In particular, the inventors of the '321 patent state that suitable prostaglandins, prostacyclins, or derivatives thereof for use in the disclosed formulations are those which possess activities as blood platelet aggregation inhibitors or anticoagulants. For example, it is stated in column 2 of the '321 patent that (lines 43 through 47):

> *"Suitable compounds of the prostacyclin/prostacyclin analog/prostaglandin series for use according to the invention are all substances which exhibit properties of inhibiting of blood platelet aggregation and are described, for example, in:..."*

As I will discuss further below, misoprostol is not known to possess activity for such a purpose (i.e., misoprostol is not known to inhibit blood platelet aggregation).

29. As mentioned by the Examiner, the inventors of the '321 patent claim as a surprising and advantageous result of their invention the fact that the joint delivery of a prostaglandin, prostacyclin or analog thereof and a thromboxane receptor antagonist for the treatment of the thrombotic and thromboembolic syndromes allows for a reduction in the dosages of these agents required as compared to typical dosage utilized for their individual administration. For example, it is stated in column 2 of the '321 patent that (lines 1 through 10):

> *"It has now been found in a surprising way that the side effects typical for PC/PCA/PG and the insufficient effectiveness of TXAA can be avoided or compensated for if PC/PCA/PG and TXAA are used jointly in the treatment of the above-mentioned syndromes. While the platelet-inhibiting antithrombotic and antithrombogenic effect of both classes of active substances is mutually potentiated, there is achieved a reduction of the cardiovascular side effects of*

PC/PCA/PG as a result of the reduction of amounts of the individual active substances possible with the combination."

Similarly, it is also stated in column 4 of the '321 patent that (lines 26 through 30):

"Amounts by weight of prostacyclin/prostacyclin analog/prostaglandin and thromboxane receptor antagonist can be used which are greatly reduced with the joint application in comparison with the necessary dosages of the individual active substances used up to now."

30. However, I disagree with the Examiner with respect to his assertion that this would motivate a skilled formulator to develop NSAID:misoprostol combination formulations in a similar manner in the hope that such a formulation would allow for the use of similar reduced dosages of misoprostol and the NSAID. Ad discussed at length in the '321 patent, both the prostaglandins, prostacyclins and derivatives thereof and the thromboxane receptor antagonists possess activity with respect to the inhibition of platelet aggregation and exert their biological effect along similar pathways.

31. For example, several pharmacological tests are described in the '321 patent examining the activities of the prostacyclin analog Iloprost and the thromboxane receptor antagonist BM 13 177 as platelet aggregation inhibitors. The first set of tests described in column 6 of the '321 patent involve an assay of the effect of Iloprost and BM 13 177 on thrombocyte function *in vitro*. With respect to the results of these tests, it is stated in column 7 of the '321 patent that (lines 1 through 24):

"Results

Iloprost, depending on the concentrations, inhibits the platelet aggregation induced by U 46 619 and the shape change. The IC_{50} for the aggregation inhibition is 1.3-2.6 nm, for the shape change inhibition the IC_{50} is 0.52-1.3 nM.

The 2^{nd} wave of the aggregation induced by ADP is inhibited with an IC_{50} of 0.26-0.65 nM depending on the concentration.

BM 13 177, depending on the concentration, inhibits the platelet aggregation induced by U 46 619 and the shape change. The IC_{50} is 1.65-6.6 microM for the aggregation, 1.65-3.3 microM for the shape change.

The 2nd wave of the aggregation induced by ADP is inhibited with an IC_{50} of 0.33-0.66 microM depending on the concentration.

Combination of thromboxane receptor antagonist and Iloprost

In the combination of BM 13 177 with Iloprost the platelet aggregation induced by U 46 619 and platelet shape change and the 2nd wave of aggregation induced by ADP are strongly inhibited in the case of concentrations of both the active substances which are on the threshold or below the threshold area. The inhibition effects of both active substances are thus potentiated (see table)."

32. Thus, one would expect that drugs that act along similar pathways to exert their biological effect could potentially act in a synergistic fashion that leads to an enhancement in their combined activity over the activity of the single drugs administered alone. In contrast for the case of NSAIDs and misoprostol, it is known that these drugs have very different activities in terms of both their pharmacological effects and their sites of action. For example, NSAIDs are anti-inflammatory and analgesic drugs that are prescribed for and act systemically as anti-inflammatory agents for the treatment of such conditions as arthritis of the joints in the body, etc. In contrast, misoprostol is a prostaglandin that is known to inhibit gastric acid secretion and increase mucosal resistance and is thus, alone and in combination formulations with NSAIDs, prescribed for the prevention of NSAID-induced gastropathy. For example, it is stated in column 1 of the '843 patent (Giset et al.) that (lines 38 through 49):

"Certain prostaglandins have been shown to prevent NSAID induced ulcers. Acceptable prostaglandin compounds for the invention herein and their preparation are described in U.S. Pat. Nos. 3,965,143, 4,060,691, 4,271,314 and 4,683,328. The prostaglandin compound commercially available under the USAN (United States Adopted Name) name misoprostol is a pharmaceutically acceptable prostaglandin which has been accepted for use in the treatment of

NSAID induced ulcers in many countries, including the United States. Misoprostol is commercially available by prescription in such countries."

33. Thus, in my opinion, a skilled formulator would have no expectation that the co-delivery of misoprostol and an NSAID would allow for a reduction in the dose of either of these two agents, since they clearly do not possess the potential to act in a synergistic fashion. This is in fact evidenced in the teachings of the '142 patent application as well as the '843 patent, the '704 patent and existing combination formulations containing misoprostol and NSAIDs such as diclofenac. In all of these cases, the disclosed combination formulations contain dosages of the NSAIDs and misoprostol that are equivalent to the dosages that are typically used for formulations of the individual drugs themselves. For example, for the case of the NSAID diclofenac, it is stated in column 4 of the '843 patent that (lines 22 through 30):

"The diclofenac can be present in any therapeutically acceptable amount. For normal pharmaceutically acceptable dosing of diclofenac, diclofenac is administered in a therapeutic dosing range using tablets containing from 25 mg to 75 mg per tablet. The Physicians' Desk Reference (PDR), 44th Edition, states that the recommended dosage for treating osteoarthritis is 100 to 150 mg per day in divided doses."

Additionally, for the case of the NSAID piroxicam, it is stated in column 4 of the '843 patent that (44 through 51):

"Currently, commercially available piroxicam tablets contain either 10 mg or 20 mg of piroxicam. The PDR, 44th Edition, recommends that piroxicam be administered in a single daily dose of 20 mg for rheumatoid arthritis and osteoarthritis. For the pharmaceutical compositions herein the inner core can contain from 10 to 20 mg of piroxicam."

For the case of misoprostol, the '843 patent teaches the use of 100 to 200 mcg of misoprostol in the disclosed combination formulations (column 2, lines 53 through 59).

34. In a similar fashion, the '142 patent application teaches loading ranges of 25 to 75 mg for diclofenac (page 4), 10 to 20 mg of piroxicam (page 5) and about 200 mcg of misoprostol (page 5). I have also made reference to the Physicians Desk Reference (2003 Online Edition, excerpts for Cytotec® and Arthrotec®, included as Exhibit E to this my Declaration) with respect to this point; the only listed formulation containing misoprostol alone (Cytotec®) describes tablets containing either 100 or 200 mcg of misoprostol for the treatment of NSAID-induced gastropathy, whereas the listed formulation containing a combination of misoprostol and diclofenac sodium (Arthrotec®) lists tablets containing either 50 or 75 mg of diclofenac sodium in combination with 200 mcg misoprostol. As a result, I disagree with the Examiner with respect to the claim that the teachings of the '321 patent would motivate a skilled formulator to develop NSAID:misoprostol combination formulations in a similar manner in the hope that such a formulation would allow for the use of similar reduced dosages of misoprostol or the NSAID.

35. As described above, the Examiner also indicates his opinion in the Final action that the use of a granulation-based manufacturing process for the production of the tablets disclosed in the '321 patent also teaches toward and makes obvious (in combination with the '507 and '939 patents) the inventions of the '142 patent application. In general, the '321 lists a wide range of dosage formulations that can be utilized in practicing the inventions disclosed therein, including tablets, capsules, suspensions, solutions and transdermal systems. For example, it is stated in column 4 of the '321 patent that (lines 51 through 54):

> *"For the preferred oral application especially tablets, dragees, capsules, pills, suspensions or solutions are suitable, which can be produced in the usual way with the additives and carrier substances customary in galenics.*

For local application, transdermal systems, for example, such as patches are used."

36. With specific respect to tablet formulations, four examples of combination tablet formulations containing the prostacyclin analog Iloprost and the thromboxane receptor antagonist identified as BM 13 77 are provided in the '321 patent. All four examples describe tablet formulations made via the conventional process of wet granulation utilizing 50% ethanolic (Examples 1 through 3) or distilled water (Example 4) as the granulating solvents. For example, with respect to Example 1 (similar statements are provided for Examples 2 through 4), it is stated in column 5 of the '321 patent that (lines 18 through 21):

"Components 3, 4 and 5 are sifted, mixed and ***granulated with the solution of 1.*** *After drying, 2 and 6 are mixed in after the other and the molding compound is molded into round tablets with an 11-mm diameter."* (Emphasis added)

37. Thus, the inventors of the '321 patent describe the use of a granulation process for the production of granules that contain the prostacyclin (Iloprost), which are then mixed with the thromboxane receptor antagonist (BM 13 177) and stearic acid and subsequently molded into tablets. As I described above, the Examiner has stated his position that the granules described in the Examples of the '321 patent are in fact "tablets" of a specific size. In particular, the Examiner states on pages 2 and 3 of the Final Action that:

"It is the examiner's position that whereas Stuerzebecher does not term granules that make up the composition "tablets", granules are tablets of a specific size, and thus makes the use of "tablets" in the instant invention obvious."

38. I disagree with this position taken by the Examiner for a number of reasons. In general, I am not aware of granules arising from a standard wet granulation process as being considered to be or called tablets in any of the standard pharmaceutical texts

concerning tablet formulation that I have encountered. As described in Chapter 37 (entitled "Granulation") of the reference edited by M. Aulton entitled "Pharmaceutics: The Science of Dosage Form Design" submitted for consideration by Counsel for the inventor of the '142 patent (the "Churchill/Livingston" reference, included as Exhibit F to this my Declaration), with respect to tablet formulation and tablets in general, granules produced by either wet or dry granulation processes are considered precursors to tablets and are not considered to be tablets themselves in any sense. For example, it is stated on page 616 of Exhibit F that:

> *"**Granulation is the process in which powder particles are made to adhere to form larger particles called granules. In the majority of cases this will be undertaken in the production of tablets or capsules, when granules will be made as an intermediate product**, but granules may also be used as a dosage form (see Chapter 17). Granulation will commence after mixing the necessary powdered ingredients so that a uniform distribution of each ingredient through the mix is achieved. **After granulation, the granules will be packed when used as a dosage form or they may be mixed with other excipients prior to tablet compression or capsule filling.**"* (Emphasis added.)

39. In my opinion, there are several other reasons as to why such granules are not considered to be tablets themselves. Tablets are generally and widely understood to be pharmaceutical dosage formulations that are required to possess a number of properties. For a given formulation, they are designed to contain a precise and reproducible amount of a drug or a combination of drugs. As described in Exhibit F and also described in other standard textbooks on tabletting technology, conventionally-produced granulations from both wet and dry processes standardly consist of a wide distribution of particle sizes. For example, it is stated on page 621 of Exhibit F that:

> *"Nuclei can grow by two possible mechanisms: either single particles can be added to the nuclei by pendular bridges or two or more nuclei may combine. The combined nuclei will be reshaped by the agitation of the bed.*

> ***This stage is characterized by the presence of a large number of small granules with a fairly wide size distribution. Providing that the size distribution is not excessively large, this point represents a suitable end-point for granules used in capsule and tablet manufacture as relatively small granules will produce a uniform tablet die or capsule fill.*** *Larger granules may give rise to problems in small diameter dies due to bridging across the die and uneven fill."* (Emphasis added.)

Thus, granules so produced would not be considered to be pharmaceutical tablets due to the wide distribution in sizes and resulting drug contents of the granules. Additionally, as indicated in the passage above from Exhibit F, the mean or median geometric diameter of the granules so produced is typically significantly smaller than the typical diameter of a pharmaceutical tablet.

40. As I described above, there are many additional standard references and textbooks relating to pharmaceutical formulation technology and tablet formulation and production that contain similar information to that contained in Exhibit F. I have included an additional example of such a reference that contains information that clearly indicates the differences and distinctions between granules produced via wet granulation and tablet dosage dorms, this being a textbook entitled "Pharmaceutics and Pharmacy Practice" edited by G. Banker and published in 1982 (included as Exhibit G to this my Declaration). For example, with respect to the required properties of pharmaceutical tablets, it is stated in Chapter 7 (entitled "Oral Drug-Delivery Systems for Prescription Pharmacy") of Exhibit G that (pages 226):

> *"Preparing Tablet Formulations for Compression. The most widely used approach to preparing the ingredients of a formulation for tablet compression is the wet granulation method.* ***The overall objective of wet granulation is to provide a granular consistency in the product that is to be compressed, with resultant suitable flow and compressibility properties."*** (Emphasis added.)

Thus, Exhibit G also teaches that granulations are produced in order to improve the flow properties and processability of a pharmaceutical formulation to enable compression or molding of the granulation into tablets.

41. In contrast, with respect to the use of granulations for the production of tablets, it is stated in Chapter 7 of Exhibit G that (pages 222 and 223):

> *"There are several important properties of tablets that are used as standards of quality control and that may, in one way or another, influence the efficacy of tablet dosage forms. These characteristics are weight variation, tablet thickness, tablet hardness, content uniformity, disintegration and dissolution."*

Clearly, granules produced via a standard wet granulation process and possessing a relatively wide distribution of particle sizes would very likely not meet any of the requirements listed above, such as uniformity of content and weight, thickness, hardness and disintegration and dissolution rates (given the known fact that granules of different sizes will disintegrate and dissolve at different rates, with smaller granules dissolving faster, etc.).

42. Additionally, such small granules would also present limitations and deficiencies with respect to ease of handling and administration by a patient and drug loading capacity within a given granule, etc., due to the small sizes of the granules. As described on page 226 of Exhibit G, wet granulations are typically formed via screening through a 6 mesh or 8 mesh screen. A 6 mesh screen is known to result in a maximum diameter cutoff of approximately 3 millimeters, which would provide for mean granulation particle diameters well below the typical minimum diameters of pharmaceutical tablets (described as 5 mm in the quote in paragraph 43 below) and also well below the size of a particle that could likely be effectively handled by a patient. Additionally, once wet granulations are dried, their mean particle sizes are typically further screened with finer mesh screens (up to 20 mesh screens as described on page 226 of Exhibit G), reducing their mean particle sizes even further.

43. In contrast, the '142 patent application discloses a novel combination tablet formulation that contains two smaller yet still pharmaceutically acceptable tablets. As described above with respect to my review of the disclosures of the '142 patent application, both the small tablets containing misoprostol (small tablet 1) and the NSAID (small tablet 2) are disclosed to be made via conventional tabletting processes. As I discussed above, Example 1 of the '142 patent application describes the production of a tablet weighing 80 mg designed to contain precisely 50.0 mg of diclofenac sodium in addition to specified amounts of microcrystalline cellulose (24.0 mg), croscarmellose sodium (5.0 mg) and magnesium stearate (1.0 mg), optionally with an enteric coating added to the tablet shell). Similarly, Example 2 of the '142 patent application describes the production of a tablet weighing 30 mg designed to contain precisely 200 μg of misoprostol dispersed in hydroxypropylmethylcellulose (20.0 mg total), microcrystalline cellulose (8.5 mg), magnesium stearate (0.5 mg) and croscarmellose sodium (1.0 mg). In my opinion, although these smaller tablets are of relatively low weights, they still clearly comprise pharmaceutical tablets. In support of this, it is also stated in Chapter 7 of Exhibit G that (page 222):

> *"Tablet weights range generally* ***from around 30 mg*** *to well over 1 g.* ***Tablet diameters usually range, as a function of tablet weight, from approximately 5 to 15 mm.*** *The weight of a tablet, of course, is made up of not only the active drug(s) but also the various tablet excipients."* (Emphasis added.)

44. Finally, as I will discuss further below with respect to the combined teachings of the '507, '321 and '939 patents, the '321 patent contains no discussions or information with respect to prostaglandin stability in the disclosed formulations. As I will discuss further below, in light of the known stability issues associated with misoprostol, in my opinion, a skilled formulator would have been taught away from formulation processes such as wet granulation for the production of dosage forms containing misoprostol.

The Disclosures and Teachings of the '939 Patent (Kararli et al.)

45. The '939 patent, entitled "Stabilized Dispersions of Misoprostol" (Kararli et al., included as Exhibit H to this my Declaration), discloses and teaches methods for the stabilization of misoprostol via formation of solid dispersions utilizing amorphous excipients and the use of the amorphous dispersions containing misoprostol in pharmaceutical formulations. Three different processes are described for production of the amorphous dispersions. For example, it is stated in column 2 of the '939 patent that (lines 32 through 38):

> *"The dispersions are generally prepared by three methods. In one method the misoprostol is solubilized in ethanol and the excipient dispersed in the solution, followed by evaporation of the solvent. In a second method water solutions of misoprostol and the excipient are lyophilized. The third method employs spray-drying of water solutions of misoprostol and the excipient."*

Similarly it is stated in column 2 of the '939 patent that (lines 42 through 50):

> *"The dispersions of the present invention can be prepared by various techniques. In the solvent method, drug is dissolved in an organic solvent, such as ethanol, and the excipient is added and mixed with the drug solution. The solvent is then evaporated. In the lyophilization method, drug and excipient are dissolved in water, the solution is frozen, then the ice is removed. In the spray drying technique, a solution of drug and excipient in water is spray dried to produce a powder dispersion."*

46. The '939 patent also teaches the use of the disclosed amorphous dispersions containing misoprostol in a wide variety of pharmaceutical dosage formulations delivered by various routes of administration, including tablets for oral administration. For example, it is stated in column 3 of the '939 patent that (lines 36 through 43):

"The dispersions can be processed, using suitable auxiliary agents or excipients, into a variety of preparations suitable for oral, nasal, intravenous, intramuscular, subcutaneous, intravaginal, buccal, ocular, transdermal, aerosol and topical pharmaceutical dosage forms for delivery of the active agent misoprostol. The dispersions can be used in production of tablets, capsules, and bead formulations for oral delivery using standard methodology."

47. In my opinion, the '939 patent simply discloses and teaches one particular set of formulation procedures for the production of stabilized amorphous dispersions containing misoprostol. However, the '939 patent does **not** (i) discuss the formulation of combination pharmaceutical dosage formulations containing both misoprostol and a NSAID, (ii) teach whether or not the disclosed amorphous dispersions containing misoprostol remain stable in the presence of a NSAID or (iii) teach towards or disclose combination tablet formulations comprised of a smaller tablet containing misoprostol in any form and a smaller tablet containing a NSAID surrounded by a shell of excipient. Thus, in my opinion, the '939 patent, read alone or in combination with the '507 and '321 patents (to be discussed below), does not make obvious the inventions disclosed in the '142 patent application.

48. In addition, I disagree with the Examiner with respect to his assertion that the teachings of the '939 patent would indicate to a skilled formulator that amorphous dispersions such as those disclosed in the '939 patent should be utilized when formulating solid pharmaceutical dosage forms containing misoprostol. Based on my review of the stability data provided in the '939 patent, I am not convinced that a skilled formulator would be taught towards the procedures disclosed in the '939 patent for the production of the amorphous dispersions containing misoprostol. For example, it is stated in column 13 of the '939 patent that (lines 30 through 33):

"The data presented in the tables show that the amorphous dispersions provide stability for misoprostol whereas those dispersions which were crystalline did not provide stability for misoprostol."

However, for the majority of the amorphous formulations claimed by the inventors of the '939 patent to display adequate stability, in my opinion, the stability data presented in the tables referred to in the quote above do not indicate that the stability is sufficient or adequate for the production of pharmaceutically acceptable dosage forms.

49. For example, FDA guidance typically requires that a given drug contained in a pharmaceutically acceptable formulation should not degrade more than 5% by weight from its preformulated weight over the shelf life of the formulation. However, many of the amorphous dispersions containing misoprostol that are claimed to demonstrate adequate stability by the inventors of the '939 patent appear to contain less than 95% of the original amount of misoprostol even at the initial timepoint (i.e., t = 0) of the stability studies. For example, the dispersions containing a combination of misoprostol and PVP (polyvinylpyrridone) made via the solvent (ethanol) method (Example 1), the lyophilization method (Example 8) and the spray drying method (Example 15) are all claimed by the inventors of the '939 patent to not display any crystallinity and to thus be stable. However, the t = 0 stability data is with respect to the percent misoprostol still present after processing is 94.3% for Example 1 (Table 1A, B, C), 89.9% for Example 8 (Table 8) and 82.1% for Example 15 (Table 14). Thus, all three techniques for the production of amorphous dispersions for the case of misoprostol:PVP appear to result in significant degradation of misoprostol during processing. Thus, it is not my opinion that a skilled formulator would be taught towards the use of these processes for the production of pharmaceutical dosage formulations containing misoprostol. Additionally, the use of these unit operations (i.e., lyophilization, spray-drying, etc.) would add complexity and cost to the production of such dosage formulations.

Combined Teachings of the '507, '321 and '939 Patents

50. As I have indicated above, upon my review of the '507, '321 and '939 patents, I have not found any disclosures or information in these patents that teaches toward or makes obvious the claimed inventions of the '142 patent application. It is also my

opinion that the combined disclosures of these three patents, when read together, do not teach towards or make obvious the claimed inventions of the '142 patent application. In my opinion, the combined teachings of these patents does not make obvious or teach towards a combination tablet formulation comprised of a smaller tablet containing misoprostol and a smaller tablet containing a NSAID surrounded by a shell of excipient which prevents exposure of the misoprostol contained therein to either the NSAID or the surface of the tablet.

51. As I discussed above, with respect to the combined teachings and disclosures of the '507, '321 and '939 patents, the Examiner states on page 3 of the Final Action that:

> *"It is the examiner's position that whereas Stuerzebecher does not term granules that make up the composition "tablets", granules are tablets of a specific size, and thus makes the use of "tablets" in the instant invention obvious. Motivation to utilize prostaglandin in combination with an NSAID such as ibuprofen would arisen in order to decrease the amount of prostaglandin and NSAID in comparison to taking the drugs separately. Furthermore, motivation to use a prostaglandin that has been dispersed in an excipient as taught by Kararli would have arisen in order to stabilize misoprostol used therein."*

As I also discussed above with respect to the above assertions made by the Examiner, it is my opinion that (i) a skilled formulator would not have considered the granules disclosed in the '321 patent to be tablets, (ii) a skilled formulator would not have expected the use of a combination of a NSAID and misoprostol to allow for the use of a decreased dose of these drug agents with respect to conventionally employed doses of the individual drugs and (iii) a skilled formulator would not necessarily have been motivated to utilize the amorphous dispersions taught in the '939 patent. Thus, I disagree with the Examiner with respect to these points.

52. Additionally, it is my opinion that a skilled formulator would not have looked to the combined teachings of these three patents due to the fact that they appear to teach in

part in different directions. For example, with respect to the stability of misoprostol in light of the combined teachings of these patents, it is taught in column 1 of the '939 patent that (lines 33 through 36):

> *"Generally, prostaglandins are difficult to formulate into stable pharmaceutical dosage forms because of their relative instability.* ***Prostaglandins tend to decompose above room temperature and in the presence of small amounts of acid, base or water.***" (Emphasis added.)

However, as I described above, the '321 patent teaches the use of wet granulation with aqueous based solvents (i.e., 50% ethanol and distilled water) for the production of granules containing a prostaglandin derivative. The use of wet granulation is known to be discouraged for formulations containing drugs that are unstable in the presence of water. For example, it is stated on page 618 of Exhibit F with respect to the use of water as a granulating solvent that:

> *"**The disadvantages of water as a solvent are that it may adversely affect drug stability, causing hydrolysis of susceptible products** and it needs a longer drying time than organic solvents."* (Emphasis added.)

53. Similarly, with respect to the combination of the teachings of the production of granules containing prostaglandin analogs in the '321 patent with respect to the teachings of combination dosage formulations containing a NSAID and misoprostol in the '507 patent, in my opinion, a skilled formulator would not look towards a process that would involve the addition of granules containing misoprostol to a formulation containing a NSAID. Due to their small size and resultant high amount of surface area per mass, the combination of granules containing misoprostol with an additional phase containing a NSAID and excipient would result in a high degree of contact between the misoprostol and the NSAID in the formulation, which would not be desired based on the known incompatibilities between misoprostol and NSAIDs discussed above. Indeed, the novel

compositions disclosed in the '142 patent application are designed and optimized to avoid and eliminate such contact between misoprostol and the NSAID.

54. Finally, as I also discussed above, a skilled formulator would not have expected the use of a combination of a NSAID and misoprostol to allow for the use of a decreased dose of these drug agents with respect to conventionally employed doses of the individual drugs, as is taught to occur for the case of prostaglandins, prostacyclins and derivatives thereof in combination with thromboxane receptor antagonists in the '321 patent. In fact, the '939 patent itself also teaches away from this. For example, it is stated in column 1 of the '939 patent that (lines 25 through 32):

> *"Misoprostol is classified in a group of compounds generally known as prostaglandins. Prostaglandins exhibit a variety of beneficial biological responses and therefore are useful as pharmaceutical agents. In particular misoprostol is a known inhibitor of gastric acid secretion and is also known to possess mucosal protective properties. Misoprostol, as a pharmaceutical agent, is therefore useful in preventing gastric ulcers."*

Thus, similar to the reasons that I described above, in my opinion, a skilled formulator would not have expected that the combination of a drug that acts to inhibit gastric acid secretion and to possess mucosal protective properties (i.e., misoprostol) would act synergistically with a NSAID to allow for a reduction in their combined doses relative to their individually administered doses.

55. In summary, I have not found any information or disclosures in the combined teachings of the '507, '321 and '949 patents that makes obvious the claimed inventions of the '142 patent application, and, in particular, Claims 1 and 2 of the '142 patent application.

Combined Teachings of the '704 and '321 Patents

56. The Examiner also states that claims 1 and 2 of the '142 patent application are obvious in light of and thus unpatentable over Franz et al. (the '704 patent) in view of Stuerzebecher et al. (the '321 patent). With respect to his interpretation of the combined teachings of these two patents, the Examiner states on pages 3 and 4 of the Final Action that:

> *"Franz teaches a sustained release pharmaceutical dosage form comprised of a capsule including bi-layer formulation made of a release layer and a buoyant layer. The release layer may consist of a NSAID such as ibuprofen, and misoprostol. Amounts of components can be 25 to 75 mg for NSAID and 100-200mm for misoprostol (col. 4, lines 4-10). These ingredients can be contained in clear, hard gelatin capsules. Franz does not teach the ingredients are tablets.*
>
> *Stuerzebecher teaches combination products containing a prostaglandin and an antagonist. The amounts of the ingredients are greatly reduced in comparison with the necessary dosages of individual active substances.*
>
> *Stuerzebecher does not term the granules that make up the composition "tablets", however it the examiner's position that the granules are tablets of a specific size. Motivation to make the bilayer of Franz in the form of Stuerzebecher would have arisen in order to greatly reduced the amounts of misoprostol and NSAID used, in comparison to the necessary dosages of the individual substances."*

57. As I describe further below, I also disagree with the examiners conclusions regarding the combined teachings of the '704 and '321 patents. In my opinion, these two patents, read alone or in combination, do not render the inventions of the '142 patent obvious. Further, it is also my opinion that these two patents (i) also teach away from each other and thus should not be read together and (ii) teach away from the inventions of the '142 patent application. Thus, I would not expect that a skilled formulator would have been motivated to follow the combined teachings of these two patents when trying

to develop a stabilized combination tablet formulation containing a NSAID and misoprostol.

58. The '704 patent, entitled "Sustained Release Bilayer Buoyant Dosage Form" (Franz et al., included as Exhibit I to this my Declaration), discloses and teaches sustained release capsule formulations of a non-compressed bilayer structure adapted to release drugs over an extended period of time in the stomach. The non-compressed bilayer capsule formulations consist of a drug release layer surrounded by a layer of excipients chosen to provide for capsule buoyancy in the stomach contents. The inventors state that these bilayer dosage formulations are designed to specifically provide for extended and complete release of the drugs contained therein in the stomach by trapping the bilayer dosage form in the stomach due to its buoyancy. For example, it is stated in column 2 of the '704 patent that (lines 43 through 62):

> *"The present invention comprises a sustained release pharmaceutical dosage form including a drug and adapted to release the drug over an extended period of time. The dosage form comprises a capsule including a non-compressed bi-layer formulation; one layer comprising a drug release layer and the other a buoyant or floating layer, the pharmaceutical dosage form providing extended gastric residence time of the bi-layer formulation so that substantially all of the drug is released in the stomach over an extended period. The dosage form has a large diameter in relation to its size and an initial density of less than 1. The floating layer of the described pharmaceutical dosage form is formulated to provide buoyancy to the dosage form and diametral increase, the floating layer including a polymer which has the properties of a gelling agent and which upon contact with gastric fluid hydrates and forms a gelatinous barrier or mass. The pharmaceutical dosage form is buoyant in gastric fluid for a period up to about 13 hours."*

59. The inventors of the '704 patent claim that combinations of misoprostol and NSAIDs are suitable for use in practicing the inventions disclosed therein. For example, it is stated in column 3 of the '704 patent that (lines 30 through 36):

> *"Some prostaglandin drugs are known to possess anti-ulcerogenic properties. Hence, it is desirable to combine or mix a prostaglandin drug having such properties, such as misoprostol, with aspirin or a non-steroidal anti-inflammatory drug (NSAID) which oftentimes exhibit ulcerogenic side effects."*

60. However, in my opinion, the disclosures of the '704 patent, read alone or in combination with the '321 patent, do not teach towards or disclose the claimed inventions of the '142 patent application. The '704 patent does not disclose nor teach towards a combination tablet formulation comprised of a smaller tablet containing misoprostol and a smaller tablet containing a NSAID surrounded and separated by a shell of excipient as is disclosed in the '142 patent application. The buoyant bilayer formulations disclosed in the '704 patent are comprised of a drug-releasing layer and a buoyancy-providing layer loosely filled sequentially into a capsule. For example, it is stated in column 6 of the '704 patent that (lines 64 through 68):

> *"The drug release layer is filled into the capsule using a conventional filling machine and the buoyancy layer is then added by free flowing the powder mixture into the capsule body. An overfilling of the buoyant layer can be used to minimize mixing of the two layers."*

The inventors of the '704 patent give no indication nor teach towards either inclusion of a drug into the buoyant layer in order to separate two drugs between layers or towards the compression of the two layers into tablets (it is likely that such compression would eliminate the generation of buoyancy of the formulation upon hydration in the stomach). Additionally, with respect to the combined teachings of the '704 and '321 patents, it is unclear as to whether the use of granules would be compatible with such a formulation.

61. Additionally, neither the '704 or '321 patents contain any discussions concerning the stability of misoprostol in such formulations, either alone or in combination with a NSAID.

62. Further, in my opinion, the '704 patent teaches away from the claimed inventions of the '142 patent application. The use of misoprostol as discussed in the '142 patent application as well as the '843, '507, '939 and '704 patents is for the treatment of gastropathy caused by the administration of NSAID drugs. Thus, in my opinion, a skilled formulator would not be motivated to utilize a formulation which would effectively increase the residence time of a NSAID in the stomach (due to the buoyancy of the formulations disclosed in the '704 patent as described above). For example, it is taught in column 3 of the '704 patent that (lines 26 through 29):

> *"Although the dosage form can be utilized with any medicament or drug it is particularly useful for acidic medicaments, prostaglandins and other drugs which are most advantageously released in the stomach."*

In contrast, it is stated on page 4 of the '142 patent application that:

> *"Preferably, the tablet containing the diclofenac or salt thereof will be* ***coated with an enteric film coating to prevent the diclofenac or salt thereof from dissolving until after it has passed through the stomach and entered the small intestine."*** (Emphasis added.)

Similarly, it is taught in column 2 of the '843 patent that (lines 40 through 52):

> *"Another embodiment of the invention herein is a pharmaceutical composition wherein a coating is provided which is an intermediate coating that surrounds the core but lies underneath the mantle coating. Such an intermediate coating can be an additional coating for preventing contact between the NSAID and prostaglandin to thereby inhibit any deleterious or otherwise non-beneficial*

interaction of the NSAID and prostaglandin such as degradation of the prostaglandin. ***Such an intermediate coating can be an enteric coating which aids in reducing the likelihood of the NSAID dissolving in the stomach and thereby directly exposing the stomach to the NSAID.*** " (Emphasis added.)

Thus, the buoyant bilayer formulations disclosed in the '704 patent appear to be incompatible with the use of an enteric coating, since the purposes of an enteric coating and a buoyant formulation are diametrically opposed. As a result, in my opinion, the '704 patent teaches away from the claimed inventions of the '142 patent application.

63. Finally, in my opinion, a skilled formulator would again not have been taught to expect the use of a combination of a NSAID and misoprostol to allow for the use of a decreased dose of these drug agents with respect to conventionally employed doses of the individual drugs based on the combined disclosures of the '704 and '321 patents. Similar to the cases described above, in my opinion, the '704 patent itself also teaches away from this result. For example, it is stated in column 1 of the '704 patent that (lines 26 through 37):

"***Prostaglandins are involved in the treatment of the pathogenesis of peptic ulcer disease. They inhibit gastric secretion in man. These antisecretory effects appear to involve a direct action on stomach parietal cells.*** *A bilayer floating dosage form is proposed to improve stomachal delivery of prostaglandins or derivatives thereof and misoprostol in particular. This should reinforce local action of prostaglandins on the parietal cells and reduce any side effects appearing when the drug is massively delivered in the intestine. Peak effects of prostaglandins will be lowered while continuously providing drug at the action sites.*" (Emphasis added.)

Again, in my opinion, a skilled formulator would not have expected that the combination of a drug that acts to inhibit gastric acid secretion via a direct action on stomach parietal cells (i.e., misoprostol) would act synergistically with a NSAID to allow for a reduction

in their combined doses relative to their individually administered doses, especially for the case of the dosage forms disclosed in the '704 patent for which the dosage form is designed to localize misoprostol to the stomach whereas the NSAID acts systemically. Additionally, the '704 patent teaches the inclusion of combinations of misoprostol and NSAIDs in the disclosed dosage forms in amounts that are conventionally utilized for their individual dosing. For example, it is stated in column 4 of the '704 patent that (lines 4 through 10):

> *"Examples of suitable NSAID's to mix or combine with a prostaglandin drug are diclofenac, piroxicam, ibuprofen or naproxen. An example of a suitable combination or mixture is diclofenac in a therapeutic amount such as from about 25 to 75 milligrams and the prostaglandin misoprostol in a therapeutic amount of from about 100 to 200 micrograms."*

64. Thus, it is my opinion that neither the combinations of the '507, '321 and '939 or the '704 and '321 teach towards or disclose the claimed inventions of the '142 patent application. As a result, I disagree with the statements made and conclusions reached by the examiner with respect to these points as described above. Further, it is also my opinion that these patents teach away from the inventions of the '142 patent application and in part teach away from each other as I have indicated above.

65. I solemnly declare and affirm further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereof.

Michael Mantle Lipp

Staff Scientist

Alkermes Inc.

AFFIRMED before me)
at Middlesex County)
in Cambridge MA, U.S.A.)
this 12th day of November, 2003)

A Commissioner, Notary Public
for taking Oaths

CINDY A. SRAGG
Notary Public
My Commission Expires
January 23, 2009

This is Exhibit A referred to in the Declaration of Dr. Michael M. Lipp, sworn this 12th day of November, 2003

A Commissioner, Notary Public
for taking oaths

CINDY A. SRAGG
Notary Public
My Commission Expires
January 23, 2005

Curriculum Vitae of Michael Mantle Lipp

Alkermes Inc.
88 Sidney St.
Cambridge, MA 02139

Telephone: (617) 250-1538
Fax Number: (617) 354-6444
Email: mike.lipp@alkermes.com

Education:

University of California, Santa Barbara, California
Ph.D. Chemical Engineering, October, 1997
Research Advisor: Professor Joseph A. Zasadzinski
Thesis Topic: " Microscopy of model lung surfactant monolayers"

Cornell University, Ithaca, New York
B.S. Chemical Engineering, May 1992
Graduated with distinction
Engineering Cooperative Program Participant, 1990

Experience:

Staff Scientist, July, 2001 - present
Pulmonary Formulations Division - Advanced Inhalation Research (AIR, a subsidiary of Alkermes - for company information, please see www.alkermes.com)
Supervisor: Dr. Jeff Hrkach (Director, Pulmonary Formulations)
Positions/Focus Areas:

* **Formulation and Feasibility Team Leadership**
  - > Formulation – selection and testing of excipients and excipient combinations for current and new AIR product formulations
  - > Production – coordination of research scale spray-drying for the production and optimization of AIR powder formulations
  - > Investigation of novel particle production methods and particle applications
  - > Conduction and coordination of feasibility studies for partnered and proprietary new AIR drug formulation candidates
* **Solid State Analysis Team Leadership**
  - > Coordination and conduction of solid-state analyses of AIR pulmonary formulations and Alkermes injectable formulations
  - > Provide information for formulation optimization and determination of developmental history for AIR project teams (physical stability studies, comparability studies, etc.)
  - > Skills/methods utilized – DSC, TGA, HPLC, SEM, vapor sorption analysis, surface area analysis, particle sizing and density determination, etc.
* **CMC Team Leadership**
  - > Experience with CMC team leadership (two small molecule project teams)
  - > Experience with IND submissions, cGMP practices, specification setting, stability study protocol determination, etc.

* **AIR Intellectual Property Technical Coordinator**
  > Interface with Alkermes Inc. Intellectual Property Department and AIR Project Teams with respect to AIR intellectual property issues
  > Provide scientific and technical evaluations of patents for the Alkermes Inc. Intellectual Property Department

Senior Scientist II, May, 2000 – June, 2001
Aerosol Science and Engineering Division - Advanced Inhalation Research
Positions:
* AIR Biomaterials Team Leader
  Responsibilities:
  > Team Leadership - manage and direct multidisciplinary team (team includes members of Engineering, Pharmaceutical Sciences, Life Sciences Divisions, etc.)
  > Preformulation and formulation of candidate AIR powder formulations
  > Solid State Characterization - manage and conduct AIR in-house and out-sourced solid state particle characterization efforts
  > New Applications - investigation of novel particle production methods and particle applications
* Powder Science and Technology Team Leader (Engineering Division sub-team)
  Responsibilities:
  > Team Leadership - manage efforts of Engineering Division Research Associate team members
  > Coordinate and conduct preformulation work for new drug formulations
  > Develop in vitro methods for monitoring particle stability and drug release
  > Develop and optimize spray-drying methods for particle production
* Aerosol Science and Engineering Group Member
  Responsibilities:
  > Feasibility and development powder production, optimization and characterization
  > Liason with Manufacturing, Pharmaceutical Sciences and Life Sciences teams.
* AIR Research Projects Team Leader
  Responsibilities:
  > Management and direction of AIR research projects
  > Management of several AIR-academic collaborative efforts
  > Supervisor - Dr. David Edwards (President/CSO - AIR)
* AIR Intellectual Property Representative/Coordinator

Senior Scientist, September 1998 - April, 2000
Aerosol Science and Engineering Division - Advanced Inhalation Research
Positions/Focus Areas:
* Powder Science and Technology Team Leader (Engineering Division sub-team)
* Team Member - Controlled Release
* Team Member: New Technology Evaluation
* Aerosol Science and Engineering Group Member

Research Affiliate, September 1998 - present
Department of Chemical Engineering
Massachusetts Institute of Technology

Positions/Focus Areas:
* Research Area: Study of lipid-based drug delivery systems
* Consultant: Assist Dr. Robert S. Langer in his role as an expert consultant/witness for various companies with respect to patent-related issues

Advisor: Professor Robert Langer

Post-Doctoral Research Fellow, February 1998-September 1998
Department of Chemical Engineering
Massachusetts Institute of Technology
Research Area: Study of large porous lipid-based particles for pulmonary drug delivery
Advisors: Professors Robert Langer (MIT) and David Edwards (Penn. State University)

Post-Doctoral Research Fellow, October 1997-January 1998
Department of Chemical Engineering
University of California, Santa Barbara, California
Research Area: Study of synthetic lung surfactant via Fluorescence, Brewster Angle, and Atomic Force Microscopy
Advisor: Professor Joseph A. Zasadzinski

Research Assistant, Ph.D. Program 1992-1997
Department of Chemical Engineering
University of California, Santa Barbara, California
Research Area: Study of synthetic lung surfactant via Fluorescence, Brewster Angle, and Atomic Force Microscopy
Advisor: Professor Joseph A. Zasadzinski

Undergraduate Research Assistant, 1991-1992
Chemical Engineering Department
Cornell University, Ithaca, New York
Research Area: Surface science of semiconductor crystal growth
Advisor: Professor James R. Engstrom

Engineering Cooperative Program, Fall, 1990
Department of Energy Science and Engineering Research Semester
Oak Ridge National Laboratory, Oak Ridge, Tennessee
Research Area: Design of an energy system for a proposed lunar base, sponsored by NASA
Advisor: Dr. Mitchell Olszewski

Awards:

National Institutes of Health NRSA Individual Postdoctoral Fellowship, 1998-2000

Lancaster Award - Top thesis in Mathematical and Physical Sciences and Engineering, University of California, Santa Barbara, 1998

Corning Foundation Materials Research Graduate Student Fellowship, 1996-1997

Materials Research Society Graduate Student Award Winner, 1996

Microscopy Society of America Presidential Student Award Winner, 1996

University of California Regents Special Fellowship, 1992-1996

Publications:

1. Phase and Morphology Changes in Lipid Monolayers Induced by SP-B Protein and its Amino-Terminal Peptide
   M. Lipp, K. Lee, J. Zasadzinski, and A. Waring, Science, 273: 1196-1199 (1996).

2. Solving Medical Problems with Chemical Engineering
   M. Lipp, K. Lee, J. Zasadzinski, and A. Waring, Chemtech, 3: 42-57 (1997).

3 Fluorescence, Polarized Fluorescence, and Brewster Angle Microscopy of Palmitic Acid and Lung Surfactant Protein B Monolayers
   M. Lipp, K. Lee, J. Zasadzinski, and A Waring, Biophysical Journal, 72:2783-2804 (1997).

4. Design and Performance of an Integrated Fluorescence, Polarized Fluorescence, and Brewster Angle Microscope/Langmuir Trough Assembly for the Study of Lung Surfactant Monolayers
   M. Lipp, K. Lee, J. Zasadzinski, and A. Waring, Review of Scientific Instruments, 68: 2574-2582 (1997).

5. Effects of Lung Surfactant Specific Protein SP-B and Model SP-B Peptide on Lipid Monolayers at the Air-Water Interface
   K. Lee, M. Lipp, J. Zasadzinski, and A. Waring, Colloids and Surfaces A, 128: 225-242 (1997).

6. Protein and Lipid Interactions in Lung Surfactant Monolayers
   M. Lipp, K. Lee, J. Zasadzinski, and A. Waring, Progress in Colloid and Polymer Science, 103: 268-279 (1997).

7. Direct Observation of Phase and Morphology Changes Induced by Lung Surfactant Protein SP-B in Lipid Monolayers via Fluorescence, Polarized Fluorescence, Brewster Angle and Atomic Force Microscopies
   K. Lee, M. Lipp, D. Takamoto, J. Zasadzinski, and A. Waring, Laser Techniques for

Condensed-Phase and Biological Systems, 3273:115-133 (1998).

8. An Apparatus for the Continuous Monitoring of Surface Morphology via Fluorescence Microscopy During Monolayer Transfer to Substrates
K. Lee, M. Lipp, D. Takamoto, E. Ter-Ovanesyan, J. Zasadzinski, and A. Waring, Langmuir, 14: 2567-2572 (1998).

9. The Incorporation of Lung Surfactant Specific Protein SP-B into Lipid Monolayers at the Air-Fluid Interface: A Synchrotron X-ray Study.
K. Lee, J. Majewski, T. Kuhl, P. Howes, K. Kjaer, M. Lipp, A. Waring, J. Zasadzinski, G. Smith, Biophysical Journal, 76 (1): A216-A216 Part 2 (1999).

10. Coexistence of Buckled and Flat Monolayers
M. Lipp, K. Lee, D. Takamoto, J. Zasadzinski, and A Waring, Physical Review Letters, 81: 1650-1653 (1999).

11. Collapse Mechanism in the Lung Surfactant System.
K. Lee, M. Lipp, D. Takamoto, J. Zasadzinski, A. Waring, Abstracts of Papers of the American Chemical Society, 216: 288-Coll. , Pt. 1 August (1998).

12. Incorporation of Lung Surfactant Specific Protein SP-B into Lipid Monolayers at the Air-Fluid Interface: A Synchrotron X-Ray Study.
K. Lee, J. Majewski, K. Kjaer, P. Howes, M. Lipp, A. Waring, J. Zasadzinski, Biophysical Journal, 76: (1): A216, January (1999).

13. Production and Characterization of Large Porous Particles for Pulmonary Drug Delivery
R. Batycky, J. Nice, D. Chen, J. Sung, M. Lipp, J. Mintzes, C. Dunbar, R. Niven, and D. Edwards, Materials Research Society Symposium Proceedings Volume 550 (1999).

14. Fractal-Dimension Particles for Drug Delivery
D. Edwards, J. Wright M. Lipp, R. Batycky, Abstracts of Papers of the American Chemical Society, 219:81-Coll., Pt. 1 March 26 (2000).

15. Conformational Mapping of the N-terminal Segment of Surfactant Protein B in Lipid Using 13C-enhanced Fourier Transform Infrared Spectrocopy
A. Waring, L. Gordon, J. Zasadzinski, F. Walther, M. Lipp, M. Sherman, K. Lee, Journal of Peptide Research, 55: (4) 330-347 April (2000).

16. The Incorporation of Lung Surfactant Specific Protein SP-B into Lipid Monolayers at the Air-Fluid Interface: A Grazing Incidence X-ray Diffraction Study
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17. Sciatic Nerve Blockade With Lipid-Protein-Sugar Particles Containing Bupivacaine
D. Kohane, M. Lipp, R.. Kinney, N. Lotan, R. Langer, Sixth World Biomaterials Conference, Kamuela, Hawaii, May 15-20 (2000).

18. Sciatic Nerve Blockade With Lipid-Protein-Sugar Particles Containing Bupivacaine
D. Kohane, M. Lipp, R.. Kinney, N. Lotan, R. Langer, Pharmaceutical Research, 17 (10): 1243-1249 (2000).

19. Effects of Lung Surfactant Proteins, SP-B and SP-C, and Palmitic Acid on Monolayer Stability
J. Ding, D. Takamoto, A. von Nahmen, M. Lipp, K. Lee, A. Waring and J. Zasadzinski, Biophysical Journal, 80 (5): 2262-2272 (2001).

20. Synchrotron X-Ray Study of Lung Surfactant-Specific Protein SP-B in Lipid Monolayers
K. Lee, J. Majewski, T. Kuhl, P. Howes, K. Kjaer, M. Lipp, A. Waring, J. Zasadzinski, and G. Smith, Biophysical Journal 81 (1), 572-585 (2001).

21. Interaction of Lung Surfactant Proteins with Anionic Phospholipids
D. Takamoto, M. Lipp, A.von Nahmen, K. Lee, A. Waring and J. Zasadzinski, Biophysical Journal 81 (1), 153-169 (2001).

22. Biocompatibility of Lipid-Protein-Sugar Particles Containing Bupivacaine in the Epineurium
D. Kohane, M. Lipp, R. Kinney, D. Anthony, D. Louis, N. Lotan, R. Langer, Journal of Biomedical Materials Research, 59 (3): 450-459 (2002).

Patents and Published Patent Applications:

1. *Use of Simple Amino Acids to Form Porous Particles*, R. Batycky, M. Lipp, R. Niven, U.S. Patent No. 6,586,008 (July 1, 2003).

2. *Modulation of Release from Dry Powder Formulations*, S. Basu, J. Hrkach, G. Caponetti, M. Lipp, K. Elbert, W. Li, U.S. Application No. 20010036481, (November 1, 2001).

3. *Lipid-Protein-Sugar Particles for Drug Delivery*, D. Kohane, M. Lipp, R. Langer, U.S. Application No. 20020150621 (October 17, 2002).

4. *Particles for Inhalation Having Sustained Release Properties*, S. Basu, J. Hrkach, M. Lipp, K. Elbert, D. Edwards, U.S. Application No. 20030118513, (June 26, 2003).

5. *Particulate Compositions for Pulmonary Delivery,* R. Batycky, D. Edwards, M. Lipp, U.S. Application No. 20030129139 (July 10, 2003).

6. *Particulate Compositions for Improving Solubility of Poorly Soluble Agents,* R. Batycky, G. Grandolfi, S. Plunkett, M. Lipp, J. Wright, U.S. Application No. 20030129250 (July 10, 2003).

This is Exhibit B referred to in the Declaration of Dr. Michael M. Lipp, sworn this 12th day of November, 2003

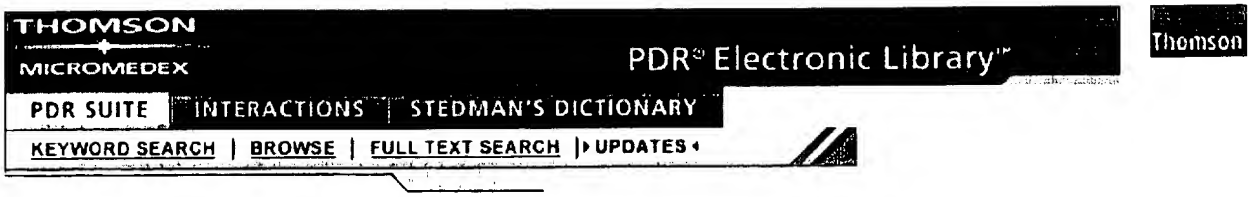
A Commissioner, Notary Public
for taking oaths

CINDY A. SRAGG
Notary Public
My Commission Expires
January 23, 2009

This is Exhibit E referred to in the Declaration of Dr. Michael M. Lipp, sworn this 12th day of November, 2003

A Commissioner, Notary Public
for taking oaths

CINDY A. SRAGG
Notary Public
My Commission Expires
January 23, 2009



Updates

The PDR Electronic Library includes:

- PDR Suite:
  - Physicians' Desk Reference 2003, Supplement B
  - PDR for Non-Prescription Drugs and Dietary Supplements 2003
  - PDR for Ophthalmic Medicines 2003
- PDR for Herbal Medicines 2002
- Stedman's Medical Dictionary, 27th Edition

All updates are incorporated into the main database on a monthly basis, so they will be found on searches.

Updates since the last print release include:

Abilify Tablets (Bristol-Myers Squibb)

Amevive for Injection (Biogen)

Augmentin XR Tablets (GlaxoSmithKline)

Avandamet Tablets (GlaxoSmithKline)

Cancidas for Injection (Merck)

Cardene I.V. (ESP Pharma)

Cenestin Tablets, 0.3mg (Duramed)

Cenestin Tablets, 0.625mg, 0.9mg, 1.25mg (Duramed)

Copegus Tablets (Roche Laboratories)

Depakote ER Tablets (Abbott)

Humira Injection (Abbott)

Kytril Injection (Roche Laboratories)

Lofibra Capsules (Gate)

Metaglip Tablets (Bristol-Myers Squibb)

Pegasys (Roche Laboratories)

SnoreStop Extinguisher 120 Oral Sprays (Green Pharmaceuticals)

SnoreStop Maximum Strength Chewable Tablets (Green Pharmaceuticals)

Taxotere for Injection Concentrate (Aventis)

Xalatan Sterile Ophthalmic Solution (Pharmacia & Upjohn)

Zetia Tablets (M rck/Schering Plough)

Zocor Tablets (Merck)

This is Exhibit D referred to in the Declaration of Dr. Michael M. Lipp, sworn this 12th day of November, 2003

A Commissioner, Notary Public
for taking oaths

CINDY A. SRAGG
Notary Public
My Commission Expires
January 23, 2009

PDR® entry for

***SEARLE* (Searle)**
ARTHROTEC®
(diclofenac sodium and misoprostol)
Tablets

CONTRAINDICATIONS AND WARNINGS

ARTHROTEC (diclofenac sodium/misoprostol) ADMINISTRATION BY ANY ROUTE IS CONTRAINDICATED, BECAUSE ITS MISOPROSTOL COMPONENT CAN CAUSE ABORTION, IN WOMEN WHO ARE PREGNANT (See **WARNINGS** and **PRECAUTIONS**).

- Anecdotal reports have been received, primarily from Brazil, of congenital anomalies and reports of fetal death in pregnancies in which misoprostol has been used as an abortifacient.

PATIENTS MUST BE ADVISED OF THE ABORTIFACIENT PROPERTY AND WARNED NOT TO GIVE THE DRUG TO OTHERS.

UTERINE RUPTURE HAS BEEN REPORTED WHEN MISOPROSTOL WAS ADMINISTERED INTRAVAGINALLY IN PREGNANT WOMEN TO INDUCE LABOR OR TO INDUCE ABORTION BEYOND THE FIRST TRIMESTER OF PREGNANCY.

UTERINE PERFORATION HAS BEEN REPORTED FOLLOWING ADMINISTRATION OF COMBINED VAGINAL-AND-ORAL MISOPROSTOL IN PREGNANT WOMEN TO INDUCE ABORTION. IN EACH OF THESE REPORTED CASES, THE GESTATIONAL AGE OF THE PREGNANCIES WAS UNKNOWN.

ARTHROTEC should not be used in women of childbearing potential unless the patient requires nonsteroidal anti-inflammatory drug (NSAID) therapy and is at high risk of developing gastric or duodenal ulceration or for developing complications from gastric or duodenal ulcers associated with the use of the NSAID. (See *WARNINGS*). In such patients, ARTHROTEC may be prescribed if the patient:

- has had a negative serum pregnancy test within 2 weeks prior to beginning therapy.
- is capable of complying with effective contraceptive measures.
- has received both oral and written warnings of the hazards of misoprostol, the risk of possible contraception failure, and the danger to other women of child-bearing potential should the drug be taken by mistake.
- will begin ARTHROTEC only on the second or third day of the next normal menstrual period.

DESCRIPTION

ARTHROTEC is a combination product containing diclofenac sodium, a nonsteroidal anti-inflammatory drug (NSAID) with analgesic properties, and misoprostol, a gastrointestinal (GI) mucosal protective prostaglandin E_1 analog. ARTHROTEC oral tablets are white to off-white, round, biconvex and approximately 11 mm in diameter. Each tablet consists of an enteric-coated core containing 50 mg (ARTHROTEC 50) or 75 mg (ARTHROTEC 75) diclofenac sodium surrounded by an outer mantle containing 200 mcg misoprostol.

Diclofenac sodium is a phenylacetic acid derivative that is a white to off-white, virtually odorless, crystalline powder. Diclofenac sodium is freely soluble in methanol, soluble in ethanol and practically insoluble in chloroform and in dilute acid. Diclofenac sodium is sparingly soluble in water. Its chemical formula and name are:

$C_{14}H_{10}Cl_2NO_2Na$ [M.W. = 318.14] 2-[(2, 6-dichlorophenyl) amino] benzeneacetic acid, monosodium salt.

Misoprostol is a water-soluble, viscous liquid that contains approximately equal amounts of two diastereomers. Its chemical formula and name are:

$C_{22}H_{38}O_5$ [M.W. = 382.54] (±)methyl 11(alpha), 16-dihydroxy-16-methyl-9-oxoprost-13E-en-1-oate.

Inactive ingredients in ARTHROTEC include: colloidal silicon dioxide; crospovidone; hydrogenated castor oil; hydroxypropyl methylcellulose; lactose; magnesium stearate; methacrylic acid copolymer; microcrystalline cellulose; povidone (polyvidone) K-30; sodium hydroxide; starch (corn); talc; triethyl citrate.

CLINICAL PHARMACOLOGY

Pharmacodynamics and pharmacokinetics of diclofenac sodium

Diclofenac sodium is a nonsteroidal anti-inflammatory drug (NSAID). In pharmacologic studies, diclofenac sodium has shown anti-inflammatory, analgesic and antipyretic properties. The mechanism of action of diclofenac sodium, like other NSAIDs, is not completely understood but may be related to prostaglandin synthetase inhibition.

Diclofenac sodium is completely absorbed from the GI tract after fasting, oral administration. The diclofenac sodium in ARTHROTEC is in a pharmaceutical formulation that resists dissolution in the low pH of gastric fluid but allows a rapid release of drug in the higher pH environment of the duodenum. Only 50% of the absorbed dose is systemically available due to first pass metabolism. Peak plasma levels are achieved in 2 hours (range 1-4 hours), and the area under the plasma concentration curve (AUC) is dose proportional within the range of 25 mg to 150 mg. Peak plasma levels are less than dose proportional and are approximately 1.5 and 2.0 mcg/mL for 50 mg and 75 mg doses, respectively.

Plasma concentrations of diclofenac sodium decline from peak levels in a biexponential fashion, with the terminal phase having a half-life of approximately 2 hours. Clearance and volume of distribution are about 350 mL/min and 550 mL/kg, respectively. More than 99% of diclofenac sodium is reversibly bound to human plasma albumin.

Diclofenac sodium is eliminated through metabolism and subsequent urinary and biliary excretion of the glucuronide and the sulfate conjugates of the metabolites. Approximately 65% of the dose is

excreted in the urine and 35% in the bile.

Conjugates of unchanged diclofenac account for 5-10% of the dose excreted in the urine and for less than 5% excreted in the bile. Little or no unchanged unconjugated drug is excreted. Conjugates of the principal metabolite account for 20-30% of the dose excreted in the urine and for 10-20% of the dose excreted in the bile.

Conjugates of three other metabolites together account for 10-20% of the dose excreted in the urine and for small amounts excreted in the bile. The elimination half-life values for these metabolites are shorter than those for the parent drug. Urinary excretion of an additional metabolite (half-life = 80 hours) accounts for only 1.4% of the oral dose. The degree of accumulation of diclofenac metabolites is unknown. Some of the metabolites may have activity.

Pharmacodynamics and pharmacokinetics of misoprostol

Misoprostol is a synthetic prostaglandin E_1 analog with gastric antisecretory and (in animals) mucosal protective properties. NSAIDs inhibit prostaglandin synthesis. A deficiency of prostaglandins within the gastric and duodenal mucosa may lead to diminishing bicarbonate and mucus secretion and may contribute to the mucosal damage caused by NSAIDs.

Misoprostol can increase bicarbonate and mucus production, but in humans this has been shown at doses 200 mcg and above that are also antisecretory. It is therefore not possible to tell whether the ability of misoprostol to prevent gastric and duodenal ulcers is the result of its antisecretory effect, its mucosal protective effect, or both.

In vitro studies on canine parietal cells using tritiated misoprostol acid as the ligand have led to the identification and characterization of specific prostaglandin receptors. Receptor binding is saturable, reversible, and stereospecific. The sites have a high affinity for misoprostol, for its acid metabolite, and for other E type prostaglandins, but not for F or I prostaglandins and other unrelated compounds, such as histamine or cimetidine. Receptor-site affinity for misoprostol correlates well with an indirect index of antisecretory activity. It is likely that these specific receptors allow misoprostol taken with food to be effective topically, despite the lower serum concentrations attained.

Misoprostol produces a moderate decrease in pepsin concentration during basal conditions, but not during histamine stimulation. It has no significant effect on fasting or postprandial gastrin nor intrinsic factor output.

Effects on gastric acid secretion: Misoprostol, over the range of 50-200 mcg, inhibits basal and nocturnal gastric acid secretion, and acid secretion in response to a variety of stimuli, including meals, histamine, pentagastrin, and coffee. Activity is apparent 30 minutes after oral administration and persists for at least 3 hours. In general, the effects of 50 mcg were modest and shorter lived, and only the 200-mcg dose had substantial effects on nocturnal secretion or on histamine-and meal-stimulated secretion.

Orally administered misoprostol is rapidly and extensively absorbed, and it undergoes rapid metabolism to its biologically active metabolite, misoprostol acid. Misoprostol acid in ARTHROTEC reaches a maximum plasma concentration in about 20 minutes and is, thereafter, quickly eliminated with an elimination $t_{1/2}$ of about 30 minutes. There is high variability in plasma levels of misoprostol acid between and within studies, but mean values after single doses show a linear relationship with dose of misoprostol over the range of 200 to 400 mcg. No accumulation of misoprostol acid was found in multiple-dose studies, and plasma steady state was achieved within 2 days. The serum protein binding of misoprostol acid is less than 90% and is concentration-

independent in the therapeutic range.

After oral administration of radiolabeled misoprostol, about 70% of detected radioactivity appears in the urine. Maximum plasma concentrations of misoprostol acid are diminished when the dose is taken with food, and total availability of misoprostol acid is reduced by use of concomitant antacid. Clinical trials were conducted with concomitant antacid; this effect does not appear to be clinically important.

Pharmacokinetic studies also showed a lack of drug interaction with antipyrine or propranolol given with misoprostol. Misoprostol given for 1 week had no effect on the steady state pharmacokinetics of diazepam when the two drugs were administered 2 hours apart.

Pharmacokinetics of ARTHROTEC

The pharmacokinetics following oral administration of a single dose (see Table 1) or multiple doses of ARTHROTEC (diclofenac sodium/misoprostol) to healthy subjects under fasted conditions are similar to the pharmacokinetics of the two individual components.

Table 1.

MISOPROSTOL ACID Mean (SD)			
Treatment (n=36)	**C_{max} (pg/mL)**	**t_{max} (hr)**	**AUC (0-4 h) (pg·hr/mL)**
ARTHROTEC 50	441 (137)	0.30 (0.13)	266 (95)
Cytotec®	478 (201)	0.30 (0.10)	295 (143)
ARTHROTEC 75	304 (110)	0.26 (0.09)	177 (49)
Cytotec	290 (130)	0.35 (0.12)	176 (58)
DICLOFENAC Mean (SD)			
Treatment (n=36)	**C_{max} (ng/mL)**	**t_{max} (hr)**	**AUC (0-12 h) (ng·hr/mL)**
ARTHROTEC 50	1207 (364)	2.4 (1.0)	1380 (272)
Voltaren®	1298 (441)	2.4 (1.0)	1357 (290)
ARTHROTEC 75	2025 (2005)	2.0 (1.4)	2773 (1347)
Voltaren	2367 (1318)	1.9 (0.7)	2609 (1185)
SD: Standard deviation of the mean			
AUC: Area under the curve			
C_{max} : Peak concentration			
t_{max} : Time to peak concentration			

The rate and extent of absorption of both diclofenac sodium and misoprostol acid from ARTHROTEC 50 and ARTHROTEC 75 are similar to those from diclofenac sodium and misoprostol formulations each administered alone.

Neither diclofenac sodium nor misoprostol acid accumulated in plasma following repeated doses of ARTHROTEC given every 12 hours under fasted conditions. Food decreases the multiple-dose bioavailability profile of ARTHROTEC 50 and ARTHROTEC 75.

Special populations

A 4-week study, comparing plasma level profiles of diclofenac (50 mg bid) in younger (26-46 years) versus older (66-81 years) adults, did not show differences between age groups (10 patients per age group). In a multiple-dose (bid) cross-over study of 24 people aged 65 years or older, the misoprostol contained in ARTHROTEC did not affect the pharmacokinetics of diclofenac sodium.

Differences in the pharmacokinetics of diclofenac have not been detected in studies of patients with renal (50 mg intravenously) or hepatic impairment (100 mg oral solution). In patients with renal impairment (N = 5, creatinine clearance 3 to 42 mL/min), AUC values and elimination rates were comparable to those in healthy people. In patients with biopsy-confirmed cirrhosis or chronic active hepatitis (variably elevated transaminases and mildly elevated bilirubins, N = 10), diclofenac concentrations and urinary elimination values were comparable to those in healthy people.

Pharmacokinetic studies with misoprostol in patients with varying degrees of renal impairment showed an approximate doubling of $t_{1/2}$, C_{max} and AUC compared to healthy people. In people over 64 years of age, the AUC for misoprostol acid is increased.

Misoprostol does not affect the hepatic mixed function oxidase (cytochrome P-450) enzyme system in animals. In a study of people with mild to moderate hepatic impairment, mean misoprostol acid AUC and C_{max} showed approximately double the mean values obtained in healthy people. Three people who had the lowest antipyrine and lowest indocyanine green clearance values had the highest misoprostol acid AUC and C_{max} values.

CLINICAL STUDIES

Osteoarthritis

Diclofenac sodium, as a single ingredient or in combination with misoprostol, has been shown to be effective in the management of the signs and symptoms of osteoarthritis.

Rheumatoid arthritis

Diclofenac sodium, as a single ingredient or in combination with misoprostol, has been shown to be effective in the management of the signs and symptoms of rheumatoid arthritis.

Upper gastrointestinal safety

Diclofenac, and other NSAIDs, have caused serious gastrointestinal toxicity, such as bleeding, ulceration and perforation of the stomach, small intestine or large intestine. Misoprostol has been shown to reduce the incidence of endoscopically diagnosed NSAID-induced gastric and duodenal ulcers. In a 12-week, randomized, double-blind, dose response study, misoprostol 200 mcg administered qid, tid or bid, was significantly more effective than placebo in reducing the incidence of gastric ulcer in OA and RA patients using a variety of NSAIDs. The tid regimen was therapeutically equivalent to misoprostol 200 mcg qid with respect to the prevention of gastric ulcers. Misoprostol 200 mcg given bid was less effective than 200 mcg given tid or qid. The incidence of NSAID-induced duodenal ulcer was also significantly reduced with all three regimens of misoprostol compared to placebo (see Table 2).

Table 2.
Mis pr st l 200 mcg D sage Regimen

	Placeb	bid	tid	qid
Gastric ulcer	11%	6% *	3% *	3% *
Duodenal ulcer	6%	2% *	3% *	1% *
N=1623; 12 weeks. *Misoprostol significantly different from placebo (p<0.05)				

Results of a study in 572 patients with osteoarthritis demonstrate that patients receiving ARTHROTEC have a lower incidence of endoscopically defined gastric ulcers compared to patients receiving diclofenac sodium (see Table 3).

Table 3.

Osteoarthritis patients with history of ulcer or erosive disease (N=572), 6 weeks	Incidence of ulcers	
	Gastric	Duodenal
ARTHROTEC 50 tid	3% *	6%
ARTHROTEC 75 bid	4% *	3%
diclofenac sodium 75 mg bid	11%	7%
placebo	3%	1%
*Statistically significantly different from diclofenac (p<0.05)		

INDICATIONS AND USAGE

ARTHROTEC is indicated for treatment of the signs and symptoms of osteoarthritis or rheumatoid arthritis in patients at high risk of developing NSAID-induced gastric and duodenal ulcers and their complications. See *WARNINGS -- Gastrointestinal effects* for a list of factors that may increase the risk of NSAID-induced gastric and duodenal ulcers and their complications.

CONTRAINDICATIONS

See boxed **CONTRAINDICATIONS AND WARNINGS** related to misoprostol.

ARTHROTEC is contraindicated in patients with hypersensitivity to diclofenac or to misoprostol or other prostaglandins. ARTHROTEC should not be given to patients who have experienced asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylactic-like reactions to diclofenac sodium have been reported.

WARNINGS

Regarding misoprostol:

See boxed **CONTRAINDICATIONS AND WARNINGS** .

Regarding diclofenac:

Gastrointestinal (GI) effects--risk of GI ulcerati n, bleeding and perforation

Serious GI toxicity, such as inflammation, bleeding, ulceration and perforation of the stomach, small intestine or large intestine, can occur at any time, with or without warning symptoms, in patients treated with NSAIDs. Minor upper GI problems, such as dyspepsia, are common and may also occur at any time during NSAID therapy. Therefore, physicians and patients should remain alert for ulceration and bleeding, even in the absence of previous GI tract symptoms. Patients should be informed about the signs and/or symptoms and the steps to take if they occur. The utility of periodic laboratory monitoring has not been demonstrated, nor has it been adequately assessed. Only 1 in 5 patients who develop a serious upper GI adverse event on NSAID therapy is symptomatic. It has been demonstrated that upper GI ulcers, gross bleeding, or perforation, causec by NSAIDs, appear to occur in approximately 1% of patients treated for 3-6 months, and in 2-4% of patients treated for 1 year. These trends continue thus, increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short-term therapy has risk.

NSAIDs should be prescribed with extreme caution in those with a prior history of ulcer disease or GI bleeding. Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore special care should be taken in treating this population. **To minimize the potential risk for an adverse event, the lowest effective dose should be used for the shortest possible duration.** For very high-risk patients, alternate therapies that do not involve NSAIDs should be considered.

Studies have shown that patients with a history of peptic ulcer disease and/or GI bleeding, and who use NSAIDs, have a greater than 10-fold risk for developing a GI bleed than patients with neither of these risk factors. In addition to a past history of ulcer disease, pharmacoepidemiological studies have identified several other conditions or co-therapies that may increase the risk for GI bleeding, such as: treatment with oral corticosteroids, treatment with anticoagulants, longer duration of NSAID therapy, older age, smoking, alcoholism, poor general health and *Helicobacter pylori* positive status.

Hepatic effects

Elevations of one or more liver tests may occur during ARTHROTEC therapy. These laboratory abnormalities may progress, may remain unchanged, or may be transient with continued therapy. Borderline elevations (ie, less than 3 times the ULN [ULN = the upper limit of the normal range]), or greater elevations of transaminases occurred in about 15% of diclofenac-treated patients. Of the hepatic enzymes, ALT (SGPT) is the one recommended for the monitoring of liver injury.

In clinical trials, meaningful elevations (ie, more than 3 times the ULN) of AST (SGOT) (ALT was not measured in all studies) occurred in about 2% of approximately 5,700 patients at some time during diclofenac treatment. In a large, open, controlled trial, meaningful elevations of ALT and/or AST occurred in about 4% of 3,700 patients treated for 2-6 months, including marked elevations (ie, more than 8 times the ULN) in about 1% of the 3,700 patients. In that open-label study, a higher incidence of borderline (less than 3 times the ULN), moderate (3-8 times the ULN), and marked (>8 times the ULN) elevations of ALT or AST was observed in patients receiving diclofenac when compared to other NSAIDs. Transaminase elevations were seen more frequently in patients with osteoarthritis than in those with rheumatoid arthritis.

In addition to enzyme elevations seen in clinical trials, postmarketing surveillance has found rare cases of severe hepatic reactions, including liver necrosis, jaundice, and fulminant fatal hepatitis with and without jaundice. Some of these rare reported cases underwent liver transplantation.

Physicians should measure transaminases periodically in patients receiving long-term therapy with diclofenac, because severe hepatotoxicity may develop without a prodrome of distinguishing symptoms. The optimum times for making the first and subsequent transaminase measurements

are not known. In the largest U.S. trial (open-label) that involved 3,700 patients monitored first at 8 weeks and 1,200 patients monitored again at 24 weeks, almost all meaningful elevations in transaminases were detected before patients became symptomatic. In 42 of the 51 patients in all trials who developed marked transaminase elevations, abnormal tests occurred during the first 2 months of therapy with diclofenac. Postmarketing experience has shown severe hepatic reactions can occur at any time during treatment with diclofenac. Cases of drug-induced hepatotoxicity have been reported in the first month, and in some cases, the first 2 months of therapy. Based on these experiences, transaminases should be monitored within 4 to 8 weeks after initiating treatment with diclofenac (see *PRECAUTIONS -- Laboratory tests*).

In clinical trials with ARTHROTEC, meaningful elevation of ALT (SGPT, more than 3 times the ULN) occurred in 1.6% of 2,184 patients treated with ARTHROTEC and in 1.4% of 1,691 patients treated with diclofenac sodium. These increases were generally transient, and enzyme levels returned to within the normal range upon discontinuation of ARTHROTEC therapy. The misoprostol component of ARTHROTEC does not appear to exacerbate the hepatic effects caused by the diclofenac sodium component. As with other NSAID containing products, if abnormal liver tests persist or worsen, if clinical signs and/or symptoms consistent with liver disease develop, or if systemic manifestations occur (eg, eosinophilia, rash, etc), ARTHROTEC should be discontinued immediately.

To minimize the possibility that hepatic injury will become severe between transaminase measurements, physicians should inform patients of the warning signs and symptoms of hepatotoxicity (eg, nausea, fatigue, lethargy, pruritus, jaundice, right upper quadrant tenderness, and "flu-like" symptoms), and the appropriate action patients should take if these signs and symptoms appear.

Anaphylactoid reactions

As with other NSAID containing products, anaphylactoid reactions may occur in patients without known prior exposure to ARTHROTEC or its components. ARTHROTEC should not be given to patients with the aspirin triad. The triad typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other NSAIDs (see *CONTRAINDICATIONS* and *PRECAUTIONS -- Preexisting asthma*). Emergency help should be sought in cases where an anaphylactoid reaction occurs. Allergic reactions have been reported by less than 0.1% of patients who received ARTHROTEC in clinical trials, and there have been rare reports of anaphylaxis in the marketed use of ARTHROTEC outside of the United States.

Advanced renal disease

In patients with advanced kidney disease, treatment with ARTHROTEC is not recommended. If NSAID therapy must be initiated however, close monitoring of the patient's kidney function is advisable (see *PRECAUTIONS -- Renal effects*).

PRECAUTIONS

Information for patients

Patients should be advised of the following:

> **SPECIAL NOTE FOR WOMEN: ARTHROTEC c ntains mis pr st l. Because f its ab rtifacient pr perty, mis pr st l is contraindicated for use by pregnant women. Misoprost l may cause miscarriage if given t pregnant women at any time during pregnancy. Miscarriages caused by misoprostol may be**

incomplete, which could lead to dangerous bleeding, hospitalization, surgery, infertility, or maternal or fetal death.

See *PATIENT INFORMATION* at the end of this labeling for important information to discuss with the patient.

ARTHROTEC is available only as a unit-of-use package that includes a leaflet containing patient information. The patient should read the leaflet before taking ARTHROTEC and each time the prescription is renewed because the leaflet may have been revised. Keep ARTHROTEC out of the reach of children.

General

ARTHROTEC cannot be used to substitute for corticosteroids or to treat for corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to disease exacerbation. Patients on prolonged corticosteroid therapy should have their therapy tapered slowly if a decision is made to discontinue corticosteroids.

The pharmacological activity of ARTHROTEC in reducing inflammation may diminish the utility of this diagnostic sign in detecting complications of presumed noninfectious, painful conditions.

Renal effects

Caution should be used when initiating treatment with ARTHROTEC in patients with considerable dehydration. It is advisable to rehydrate patients first and then start therapy with ARTHROTEC. Caution is also recommended in patients with preexisting kidney disease (see *WARNINGS -- Advanced renal disease*).

As with other NSAIDs, long-term administration of diclofenac has resulted in renal papillary necrosis and other renal medullary changes. Renal toxicity has also been seen in patients in which renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of an NSAID may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, or liver dysfunction, those taking diuretics and ACE inhibitors, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state.

Diclofenac metabolites are eliminated primarily by the kidneys. The extent to which the metabolites may accumulate in patients with renal failure has not been studied. As with other NSAIDs, metabolites of which are excreted by the kidney, patients with significantly impaired renal function should be more closely monitored.

Hematologic effects

Anemia is sometimes seen in patients receiving diclofenac or other NSAIDs. This may be due to fluid retention, GI blood loss, or an incompletely described effect upon erythropoiesis. Patients on long-term treatment with NSAIDs, including ARTHROTEC, should have their hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anemia.

All drugs that inhibit the biosynthesis of prostaglandins may interfere to some extent with platelet function and vascular responses to bleeding.

NSAIDs inhibit platelet aggregation and, unlike aspirin, their effect on platelet function is reversible,

quantitatively less, and of shorter duration. ARTHROTEC does not generally affect platelet counts, prothrombin time (PT), or partial thromboplastin time (PTT). Patients receiving ARTHROTEC who may be adversely affected by alterations in platelet function, such as those with coagulation disorders or patients receiving anticoagulants, should be carefully monitored.

Aseptic meningitis

As with other NSAIDs, aseptic meningitis with fever and coma has been observed on rare occasions in patients on diclofenac therapy. Although it is probably more likely to occur in patients with systemic lupus and related connective tissue diseases, it has been reported in patients who do not have an underlying chronic disease. If signs or symptoms of meningitis develop in a patient on diclofenac, the possibility of its being related to diclofenac should be considered.

Fluid retention and edema

Fluid retention and edema have been observed in some patients taking NSAID containing products, including ARTHROTEC. Therefore, as with other NSAID containing products, ARTHROTEC should be used with caution in patients with a history of cardiac decompensation, hypertension, or other conditions predisposing to fluid retention.

Preexisting asthma

Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthma has been associated with severe bronchospasm, which can be fatal. Since cross-reactivity, including bronchospasm, between aspirin and other NSAIDs has been reported in such aspirin-sensitive patients, ARTHROTEC should not be administered to patients with this form of aspirin sensitivity and should be used with caution in patients with preexisting asthma.

Porphyria

The use of ARTHROTEC in patients with hepatic porphyria should be avoided. To date, one patient has been described in whom diclofenac sodium probably triggered a clinical attack of porphyria. The postulated mechanism, demonstrated in rats, for causing such attacks by diclofenac sodium, as well as some other NSAIDs, is through stimulation of the porphyrin precursor delta-aminolevulinic acid (ALA).

Laboratory tests

Patients on long-term treatment with NSAIDs should have their CBC and a chemistry profile checked periodically. If clinical signs and symptoms consistent with liver or renal disease develop, systemic manifestations occur (eg, eosinophilia, rash, etc) or if abnormal liver tests persist or worsen, ARTHROTEC should be discontinued.

Effect on blood coagulation: Diclofenac sodium impairs platelet aggregation but does not affect bleeding time, plasma thrombin clotting time, plasma fibrinogen, or factors V and VII to XII. Statistically significant changes in prothrombin and partial thromboplastin times have been reported in normal volunteers. The mean changes were observed to be less than 1 second in both instances, however, and are unlikely to be clinically important. Diclofenac sodium is a prostaglandin synthetase inhibitor, however, and all drugs that inhibit prostaglandin synthesis interfere with platelet function to some degree; therefore, patients who may be adversely affected by such an action should be carefully observed. Misoprostol has not been shown to exacerbate the effects of diclofenac on platelet activity.

Drug interactions

Aspirin: Concomitant administration of ARTHROTEC and aspirin is not recommended because diclofenac sodium is displaced from its binding sites by aspirin, resulting in lower plasma concentrations, peak plasma levels and AUC values.

Digoxin: Elevated digoxin levels have been reported in patients receiving digoxin and diclofenac sodium. Patients receiving digoxin and ARTHROTEC should be monitored for possible digoxin toxicity.

Antihypertensive agents: NSAIDs can inhibit the activity of antihypertensives, including ACE inhibitors. Thus, caution should be taken when administering ARTHROTEC with such agents.

Warfarin: The effects of warfarin and NSAIDs on GI bleeding are synergistic, such that users of both drugs together have a risk of serious bleeding greater than users of either drug alone.

Oral hypoglycemics: Diclofenac sodium does not alter glucose metabolism in healthy people nor does it alter the effects of oral hypoglycemic agents. There are rare reports, however, from marketing experience, of changes in effects of insulin or oral hypoglycemic agents in the presence of diclofenac sodium that necessitated change in the doses of such agents. Both hypo- and hyperglycemic effects have been reported. A direct causal relationship has not been established, but physicians should consider the possibility that diclofenac sodium may alter a diabetic patient's response to insulin or oral hypoglycemic agents.

Methotrexate and cyclosporine: ARTHROTEC, like other NSAID containing products, may affect renal prostaglandins and increase the toxicity of certain drugs. Ingestion of ARTHROTEC may increase serum concentrations of methotrexate and increase cyclosporine nephrotoxicity. Patients who begin taking ARTHROTEC or who increase their dose of ARTHROTEC or any other NSAID containing product while taking methotrexate or cyclosporine may develop toxicity characteristic for these drugs. They should be observed closely, particularly if renal function is impaired.

Lithium: NSAIDs have produced an elevation of plasma lithium levels and a reduction in renal lithium clearance. The mean minimum lithium concentration increased 15% and the renal clearance was decreased by approximately 20%. These effects have been attributed to inhibition of renal prostaglandin synthesis by the NSAID. Thus, when NSAIDs and lithium are administered concurrently, subjects should be observed carefully for signs of lithium toxicity.

Antacids: Antacids reduce the bioavailability of misoprostol acid. Antacids may also delay absorption of diclofenac sodium. Magnesium-containing antacids exacerbate misoprostol-associated diarrhea. Thus, it is not recommended that ARTHROTEC be coadministered with magnesium-containing antacids.

Diuretics: The diclofenac sodium component of ARTHROTEC, like other NSAIDs, can inhibit the activity of diuretics. Concomitant therapy with potassium-sparing diuretics may be associated with increased serum potassium levels.

Other drugs: In small groups of patients (7-10 patients/interaction study), the concomitant administration of azathioprine, gold, chloroquine, D-penicillamine, prednisolone, doxycycline or digitoxin did not significantly affect the peak levels and AUC levels of diclofenac sodium. Phenobarbital toxicity has been reported to have occurred in a patient on chronic phenobarbital treatment following the initiation of diclofenac therapy. *In vitro* , diclofenac interferes minimally with the protein binding of prednisolone (10% decrease in binding). Benzylpenicillin, ampicillin, oxacillin, chlortetracycline, doxycycline, cephalothin, erythromycin, and sulfamethoxazole have no influence, *in vitro* , on the protein binding of diclofenac in human serum.

Animal toxicology

A reversible increase in the number of normal surface gastric epithelial cells occurred in the dog, rat, and mouse during long-term toxicology studies with misoprostol. No such increase has been observed in humans administered misoprostol for up to 1 year. An apparent response of the female mouse to misoprostol in long-term studies at 100 to 1000 times the human dose was hyperostosis, mainly of the medulla of sternebrae. Hyperostosis did not occur in long-term studies in the dog and rat and has not been seen in humans treated with misoprostol.

Carcinogenesis, mutagenesis, impairment of fertility

Long-term animal studies to evaluate the potential for carcinogenesis and animal studies to evaluate the effects on fertility have been performed with each component of ARTHROTEC given alone. ARTHROTEC itself (diclofenac sodium and misoprostol combinations in 250:1 ratio) was not genotoxic in the Ames test, the Chinese hamster ovary cell (CHO/HGPRT) forward mutation test, the rat lymphocyte chromosome aberration test or the mouse micronucleus test.

In a 24-month rat carcinogenicity study, oral misoprostol at doses up to 2.4 mg/kg/day (14.4 mg/m ^{2} /day, 24 times the recommended maximum human dose of 0.6 mg/m ^{2} /day) was not tumorigenic. In a 21-month mouse carcinogenicity study, oral misoprostol at doses up to 16 mg/kg/day (48 mg/m ^{2} /day), 80 times the recommended maximum human dose based on body surface area, was not tumorigenic. Misoprostol, when administered to male and female breeding rats in an oral dose-range of 0.1 to 10 mg/kg/day (0.6 to 60 mg/m ^{2} /day, 1 to 100 times the recommended maximum human dose based on body surface area) produced dose-related pre- and post-implantation losses and a significant decrease in the number of live pups born at the highest dose. These findings suggest the possibility of a general adverse effect on fertility in males and females.

In a 24-month rat carcinogenicity study, oral diclofenac sodium up to 2 mg/kg/day (12 mg/m ^{2} /day) was not tumorigenic. For a 50-kg person of average height (1.46m ^{2} body surface area), this dose represents 0.08 times the recommended maximum human dose (148 mg/m ^{2}) on a body surface area basis. In a 24-month mouse carcinogenicity study, oral diclofenac sodium at doses up to 0.3 mg/kg/day (0.9 mg/m ^{2} /day, 0.006 times the recommended maximum human dose based on body surface area) in males and 1 mg/kg/day (3 mg/m ^{2} /day, 0.02 times the recommended maximum human dose based on body surface area) in females was not tumorigenic. Diclofenac sodium at oral doses up to 4 mg/kg/day (24 mg/m ^{2} /day, 0.16 times the recommended maximum human dose based on body surface area) was found to have no effect on fertility and reproductive performance of male and female rats.

Pregnancy

Pregnancy category X: See boxed **CONTRAINDICATIONS AND WARNINGS** regarding misoprostol. One case of amniotic fluid embolism, which resulted in maternal and fetal death, has been reported with use of misoprostol during pregnancy. Severe vaginal bleeding, retained placenta, shock, fetal bradycardia, and pelvic pain have also been reported. These women were administered misoprostol vaginally and/or orally over a range of doses.

Non-teratogenic effects

Misoprostol may endanger pregnancy (may cause miscarriage) and thereby cause harm to the fetus when administered to a pregnant woman. Misoprostol produces uterine contractions, uterine bleeding, and expulsion of the products of conception. Miscarriages caused by misoprostol may be incomplete. In studies in women undergoing elective termination of pregnancy during the first

trimester, misoprostol caused partial or complete expulsion of the products of conception in 11% of the subjects and increased uterine bleeding in 41%.

Reports, primarily from Brazil, of congenital anomalies and reports of fetal death subsequent to use of misoprostol alone, as an abortifacient, have been received (see boxed **CONTRAINDICATIONS AND WARNINGS**). If a woman is or becomes pregnant while taking this drug, the drug should be discontinued and the patient apprised of the potential hazard to the fetus.

The diclofenac sodium component of ARTHROTEC, like other NSAIDs which are prostaglandin-inhibiting drugs, may affect the fetal cardiovascular system causing premature closure of the ductus arteriosus. NSAIDs may also inhibit uterine contractions.

Teratogenic effects

An oral teratology study has been performed in pregnant rabbits at dose combinations (250:1 ratio) up to 10 mg/kg/day diclofenac sodium (120 mg/m ^{2} /day, 0.8 times the recommended maximum human dose based on body surface area) and 0.04 mg/kg/day misoprostol (0.48 mg/m ^{2} /day, 0.8 times the recommended maximum human dose based on body surface area) and has revealed no evidence of teratogenic potential for ARTHROTEC.

Oral teratology studies have been performed in pregnant rats at doses up to 1.6 mg/kg/day (9.6 mg/m ^{2} /day, 16 times the recommended maximum human dose based on body surface area) and pregnant rabbits at doses up to 1.0 mg/kg/day (12 mg/m ^{2} /day, 20 times the recommended maximum human dose based on body surface area) and have revealed no evidence of teratogenic potential for misoprostol.

Oral teratology studies have been performed in pregnant mice at doses up to 20 mg/kg/day (60 mg/m ^{2} /day, 0.4 times the recommended maximum human dose based on body surface area), pregnant rats at doses up to 10 mg/kg/day (60 mg/m ^{2} /day, 0.4 times the recommended maximum human dose based on body surface area) and pregnant rabbits at doses up to 10 mg/kg/day (120 mg/m ^{2} /day, 0.8 times the recommended maximum human dose based on body surface area) and have revealed no evidence of teratogenic potential for diclofenac sodium.

Nursing mothers

Diclofenac sodium has been found in the milk of nursing mothers. It is unlikely that misoprostol is excreted into milk since the drug is rapidly metabolized throughout the body. Excretion of the active metabolite (misoprostol acid) into milk is possible, but has not been studied. Because of the potential for serious adverse reactions in nursing infants, ARTHROTEC is not recommended for use by nursing mothers.

Pediatric use

Safety and effectiveness of ARTHROTEC in pediatric patients have not been established.

Geriatric use

Of the more than 2,100 subjects in clinical studies with ARTHROTEC, 25% were 65 and over, while 6% were 75 and over. In studies with diclofenac, 31% of subjects were 65 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

As with any NSAID, the elderly are likely to tolerate adverse events less well than younger patients.

Diclofenac is known to be substantially excreted by the kidney, and the risk of toxic reactions to ARTHROTEC may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (see *PRECAUTIONS -- Renal effects*).

Based on studies in the elderly, no adjustment of the dose of ARTHROTEC is necessary in the elderly for pharmacokinetic reasons (see *Pharmacokinetics of ARTHROTEC-- Special populations*), although many elderly may need to receive a reduced dose because of low body weight or disorders associated with aging.

ADVERSE REACTIONS

Adverse reactions associated with ARTHROTEC

Adverse reaction information for ARTHROTEC is derived from Phase III multinational controlled clinical trials in over 2,000 patients, receiving ARTHROTEC 50 or ARTHROTEC 75, as well as from blinded, controlled trials of Voltaren® Delayed-Release Tablets (diclofenac) and Cytotec® Tablets (misoprostol).

Gastrointestinal

GI disorders had the highest reported incidence of adverse events for patients receiving ARTHROTEC. These events were generally minor, but led to discontinuation of therapy in 9% of patients on ARTHROTEC and 5% of patients on diclofenac. For GI ulcer rates, see *CLINICAL STUDIES -- Upper gastrointestinal safety* .

GI disorder	ARTHROTEC	Diclofenac
Abdominal pain	21%	15%
Diarrhea	19%	11%
Dyspepsia	14%	11%
Nausea	11%	6%
Flatulence	9%	4%

ARTHROTEC can cause more abdominal pain, diarrhea and other GI symptoms than diclofenac alone.

Diarrhea and abdominal pain developed early in the course of therapy, and were usually self-limited (resolved after 2 to 7 days). Rare instances of profound diarrhea leading to severe dehydration have been reported in patients receiving misoprostol. Patients with an underlying condition such as inflammatory bowel disease, or those in whom dehydration, were it to occur, would be dangerous, should be monitored carefully if ARTHROTEC is prescribed. The incidence of diarrhea can be minimized by administering ARTHROTEC with food and by avoiding coadministration with magnesium-containing antacids.

Gynecological

Gynecological disorders previously reported with misoprostol use have also been reported for women receiving ARTHROTEC (see below). Postmenopausal vaginal bleeding may be related to

ARTHROTEC administration. If it occurs, diagnostic workup should be undertaken to rule out gynecological pathology. There have been reports in which intravaginal administration of misoprostol in pregnant women resulted in rupture of the uterus and death of the infant. (See boxed **CONTRAINDICATIONS AND WARNINGS** .)

Elderly

Overall, there were no significant differences in the safety profile of ARTHROTEC in over 500 patients 65 years of age or older compared with younger patients.

Other adverse experiences reported occasionally or rarely with ARTHROTEC, diclofenac or other NSAIDs, or misoprostol are:

Body as a whole: Asthenia, death, fatigue, fever, infection, malaise, sepsis.

Cardiovascular system: Arrhythmia, atrial fibrillation, congestive heart failure, hypertension, hypotension, increased CPK, increased LDH, myocardial infarction, palpitations, phlebitis, premature ventricular contractions, syncope, tachycardia, vasculitis.

Central and peripheral nervous system: Coma, convulsions, dizziness, drowsiness, headache, hyperesthesia, hypertonia, hypoesthesia, insomnia, meningitis, migraine, neuralgia, paresthesia, somnolence, tremor, vertigo.

Digestive: Anorexia, appetite changes, constipation, dry mouth, dysphagia, enteritis, esophageal ulceration, esophagitis, eructation, gastritis, gastroesophageal reflux, GI bleeding, GI neoplasm benign, glossitis, heartburn, hematemesis, hemorrhoids, intestinal perforation, peptic ulcer, stomatitis and ulcerative stomatitis, tenesmus, vomiting.

Female reproductive disorders: Breast pain, dysmenorrhea, intermenstrual bleeding, leukorrhea, menstrual disorder, menorrhagia, vaginal hemorrhage.

Hemic and lymphatic system: Agranulocytosis, anemia, aplastic anemia, coagulation time increased, ecchymosis, eosinophilia, epistaxis, hemolytic anemia, leukocytosis, leukopenia, lymphadenopathy, melena, pancytopenia, pulmonary embolism, purpura, rectal bleeding, thrombocythemia, thrombocytopenia.

Hypersensitivity: Angioedema, laryngeal/pharyngeal edema, urticaria.

Liver and biliary system: Abnormal hepatic function, bilirubinemia, hepatitis, jaundice, liver failure, pancreatitis.

Male reproductive disorders: Impotence, perineal pain.

Metabolic and nutritional: Alkaline phosphatase increased, BUN increased, dehydration, glycosuria, gout, hypercholesterolemia, hyperglycemia, hyperuricemia, hypoglycemia, hyponatremia, periorbital edema, porphyria, weight changes.

Musculoskeletal system: Arthralgia, myalgia.

Psychiatric: Anxiety, concentration impaired, confusion, depression, disorientation, dream abnormalities, hallucinations, irritability, nervousness, paranoia, psychotic reaction.

Respiratory system: Asthma, coughing, dyspnea, hyperventilation, pneumonia, respiratory

depression.

Skin and appendages: Acne, alopecia, bruising, eczema, erythema multiforme, exfoliative dermatitis, pemphigoid reaction, photosensitivity, pruritus, pruritus ani, rash, skin ulceration, Stevens-Johnson syndrome, sweating increased, toxic epidermal necrolysis.

Special senses: Hearing impairment, taste loss, taste perversion, tinnitus.

Urinary system: Cystitis, dysuria, hematuria, interstitial nephritis, micturition frequency, nocturia, nephrotic syndrome, oliguria/polyuria, papillary necrosis, proteinuria, renal failure, urinary tract infection.

Vision: Amblyopia, blurred vision, conjunctivitis, diplopia, glaucoma, iritis, lacrimation abnormal, night blindness, vision abnormal.

OVERDOSAGE

The toxic dose of ARTHROTEC has not been determined. However, signs of overdosage from the components of the product have been described.

Diclofenac sodium

Clinical signs that may suggest diclofenac sodium overdose include GI complaints, confusion, drowsiness or general hypotonia. Reports of overdosage with diclofenac cover 66 cases. In approximately one-half of these reports of overdosage, concomitant medications were also taken. The highest dose of diclofenac was 5.0 g in a 17-year-old man who suffered loss of consciousness, increased intracranial pressure, and aspiration pneumonitis, and died 2 days after overdose. A 24-year-old woman who took 4.0 g and the 28- and 42-year-old women, each of whom took 3.75 g, did not develop any clinically significant signs or symptoms. However, there was a report of a 17-year-old female who experienced vomiting and drowsiness after an overdose of 2.37 g of diclofenac.

Animal studies show a wide range of susceptibilities to acute overdosage, with primates being more resistant to acute toxicity than rodents (LD_{50} in mg/kg: rats, 55; dogs, 500; monkeys, 3200).

Misoprostol

The toxic dose of misoprostol in humans has not been determined. Cumulative total daily doses of 1600 mcg have been tolerated, with only symptoms of GI discomfort being reported. In animals, the acute toxic effects are diarrhea, GI lesions, focal cardiac necrosis, hepatic necrosis, renal tubular necrosis, testicular atrophy, respiratory difficulties, and depression of the central nervous system. Clinical signs that may indicate an overdose are sedation, tremor, convulsions, dyspnea, abdominal pain, diarrhea, fever, palpitations, hypotension, or bradycardia.

ARTHROTEC

Symptoms of ARTHROTEC overdosage should be treated with supportive therapy. In case of acute overdosage, gastric lavage is recommended. Induced diuresis may be beneficial because diclofenac sodium and misoprostol metabolites are excreted in the urine. The effect of dialysis or hemoperfusion on the elimination of diclofenac sodium (99% protein bound) and misoprostol acid remains unproven. The use of oral activated charcoal may help to reduce the absorption of diclofenac sodium and misoprostol.

DOSAGE AND ADMINISTRATION

ARTHROTEC is administered as ARTHROTEC 50 (50 mg diclofenac sodium/200 mcg misoprostol) or as ARTHROTEC 75 (75 mg diclofenac sodium/200 mcg misoprostol).

Note: See *SPECIAL DOSING CONSIDERATIONS* section, below.

Osteoarthritis: The recommended dosage for maximal GI mucosal protection is ARTHROTEC 50 tid. For patients who experience intolerance, ARTHROTEC 75 bid or ARTHROTEC 50 bid can be used, but are less effective in preventing ulcers. This fixed combination product, ARTHROTEC, is not appropriate for patients who would not receive the appropriate dose of both ingredients. Doses of the components delivered with these regimens are as follows:

	OA regimen	Diclofenac sodium (mg/day)	Misoprostol (mcg/day)
ARTHROTEC 50	tid	150	600
	bid	100	400
ARTHROTEC 75	bid	150	400

Rheumatoid Arthritis: The recommended dosage is ARTHROTEC 50 tid or qid. For patients who experience intolerance, ARTHROTEC 75 bid or ARTHROTEC 50 bid can be used, but are less effective in preventing ulcers. This fixed combination product, ARTHROTEC, is not appropriate for patients who would not receive the appropriate dose of both ingredients. Doses of the components delivered with these regimens are as follows:

	RA regimen	Diclofenac sodium (mg/day)	Misoprostol (mcg/day)
ARTHROTEC 50	qid	200	800
	tid	150	600
	bid	100	400
ARTHROTEC 75	bid	150	400

SPECIAL DOSING CONSIDERATIONS: ARTHROTEC contains misoprostol, which provides protection against gastric and duodenal ulcers (see *CLINICAL STUDIES*). For gastric ulcer prevention, the 200 mcg qid and tid regimens are therapeutically equivalent, but more protective than the bid regimen. For duodenal ulcer prevention, the qid regimen is more protective than the tid or bid regimens. However, the qid regimen is less well tolerated than the tid regimen because of usually self-limited diarrhea related to the misoprostol dose (see *ADVERSE REACTIONS -- Gastrointestinal*), and the bid regimen may be better tolerated than tid in some patients.

Dosages may be individualized using the separate products (misoprostol and diclofenac), after which the patient may be changed to the appropriate ARTHROTEC dose. If clinically indicated, misoprostol co-therapy with ARTHROTEC, or use of the individual components to optimize the misoprostol dose and/or frequency of administration, may be appropriate. The total dose of misoprostol should not exceed 800 mcg/day, and no more than 200 mcg of misoprostol should be administered at any one time. Doses of diclofenac higher than 150 mg/day in osteoarthritis or higher than 225 mg/day in rheumatoid arthritis are not recommended.

For additional information, it may be helpful to refer to the package inserts for Cytotec® tablets and Voltaren® tablets.

HOW SUPPLIED

ARTHROTEC (diclofenac sodium/misoprostol) is supplied as a film-coated tablet in dosage strengths of either 50 mg diclofenac sodium/200 mcg misoprostol or 75 mg diclofenac sodium/200 mcg misoprostol. The 50 mg/200 mcg dosage strength is a round, biconvex, white to off-white tablet imprinted with four "A's" encircling a "50" in the middle on one side and "SEARLE" and "1411" on the other. The 75 mg/200 mcg dosage strength is a round, biconvex, white to off-white tablet imprinted with four "A's" encircling a "75" in the middle on one side and "SEARLE" and "1421" on the other.

The dosage strengths are supplied in:

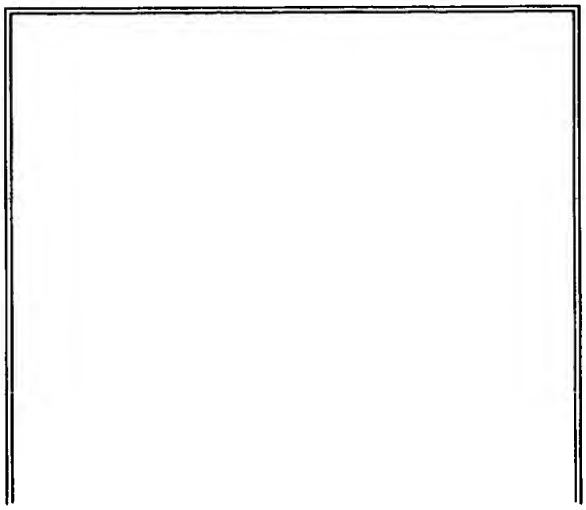
Strength	NDC Number	Size
50/200	0025-1411-60	bottle of 60
	0025-1411-90	bottle of 90
	0025-1411-34	carton of 100 unit dose
75/200	0025-1421-60	bottle of 60
	0025-1421-34	carton of 100 unit dose

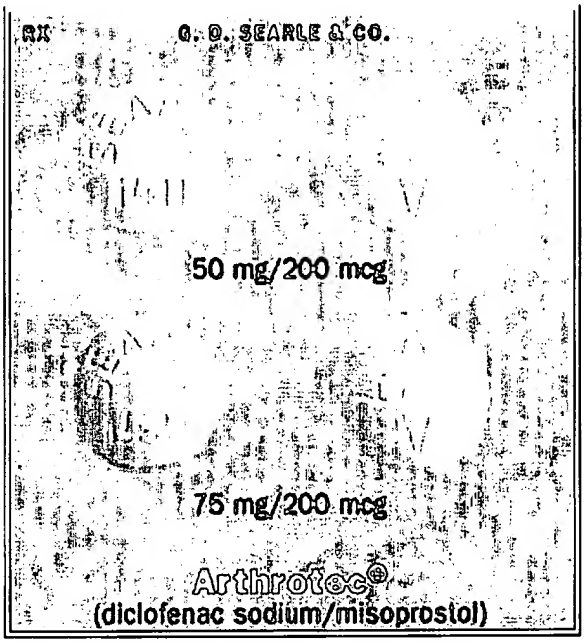
Store at or below 25°C (77°F), in a dry area.

PRODUCT PHOTO(S):

NOTE: These photos can be used only for identification by shape, color, and imprint. They do not depict actual *or relative* size.

The product samples shown here have been supplied by the manufacturer and reproduced in full color by PDR as a quick-reference identification aid. While every effort has been made to assure accurate reproduction, please remember that any visual identification should be considered preliminary. In cases of poisoning or suspected overdosage, the drug's identity should be verified by chemical analysis.





PATIENT INFORMATION

Read this leaflet before taking ARTHROTEC (diclofenac sodium 50 or 75 mg/misoprostol 200 mcg) and each time your prescription is renewed, because the leaflet may be changed.

ARTHROTEC is being prescribed by your doctor for treatment of your arthritis symptoms while at the same time providing protection from the development of stomach and intestinal ulcers due to the arthritis medication. ARTHROTEC contains diclofenac, an arthritis medication. ARTHROTEC also contains misoprostol to decrease the chance of getting stomach and intestinal ulcers that sometimes develop with NSAID medications. Serious side effects are still possible, however, and you should report to your physician any signs or symptoms of gastrointestinal ulceration or bleeding, skin rash, weight gain or swelling. If signs of liver toxicity occur (nausea, fatigue, lethargy, itching, jaundice, right upper quadrant tenderness, and "flu-like" symptoms) you should stop therapy and seek immediate medical attention.

Do not take ARTHROTEC if you are pregnant, because it contains misoprostol which can cause miscarriage if given at any stage of pregnancy. It is also important to avoid pregnancy while taking this medication and for at least one month or through one menstrual cycle after you stop taking it. Misoprostol may cause the uterus to rupture (tear) in pregnant women if it is used to bring on (induce) labor or to cause an abortion after the first trimester of pregnancy. Miscarriages or rupture of the uterus may result in severe bleeding, hospitalization, surgery, infertility or death.

If you become pregnant during ARTHROTEC therapy, stop taking ARTHROTEC and contact your doctor immediately. Remember that even if you are using a means of birth control, it is still possible to become pregnant. Should this occur, stop taking ARTHROTEC and consult your physiciar immediately.

ARTHROTEC may cause diarrhea, abdominal pain, upset stomach and/or nausea in some people. In most cases these problems develop during the first few weeks of therapy and stop after about a week with continued treatment. You can minimize possible diarrhea by making sure you take ARTHROTEC with meals and by avoiding the use of antacids containing magnesium (if needed, use one containing aluminum or calcium instead). ARTHROTEC tablets should be swallowed whole, and

not chewed, crushed or dissolved.

Because these side effects are usually mild to moderate and usually go away in a matter of days, most patients can continue to take ARTHROTEC. If you have prolonged difficulty (more than 7 days), or if you have severe diarrhea, cramping and/or nausea, call your doctor.

Take ARTHROTEC only according to the directions given by your doctor. Changes in dose should be made only with your doctor's approval.

Do not give ARTHROTEC to anyone else. It has been prescribed for your specific condition, may not be the correct treatment for another person, and could be dangerous for another person, especially a woman who may be, or could become, pregnant.

This information sheet does not cover all possible side effects of ARTHROTEC. See your doctor if you have questions. Keep out of reach of children.

Rx only Revised: Mar. 6, 2000

Pkgd. by Searle & Co., San Juan PR 00936

Manufactured by Searle, Morpeth, England

For G.D. Searle & Co.

Chicago IL 60680 USA

Address medical inquiries to:

G.D. Searle & Co.

Healthcare Information Services

5200 Old Orchard Road

Skokie IL 60077

SEARLE

Arthrotec®

(diclofenac sodium and misoprostol)

Tablets

A05440-6

PDR® entry for

CYTOTEC® (Searle)
misoprostol tablets

WARNINGS

CYTOTEC (MISOPROSTOL) ADMINISTRATION TO WOMEN WHO ARE PREGNANT CAN CAUSE ABORTION, PREMATURE BIRTH, OR BIRTH DEFECTS. UTERINE RUPTURE HAS BEEN REPORTED WHEN CYTOTEC WAS ADMINISTERED IN PREGNANT WOMEN TO INDUCE LABOR OR TO INDUCE ABORTION BEYOND THE EIGHTH WEEK OF PREGNANCY (see also **PRECAUTIONS** and **LABOR AND DELIVERY**). CYTOTEC SHOULD NOT BE TAKEN BY PREGNANT WOMEN TO REDUCE THE RISK OF ULCERS INDUCED BY NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs) (see **CONTRAINDICATIONS** , **WARNINGS** , and **PRECAUTIONS**).

PATIENTS MUST BE ADVISED OF THE ABORTIFACIENT PROPERTY AND WARNED NOT TO GIVE THE DRUG TO OTHERS.

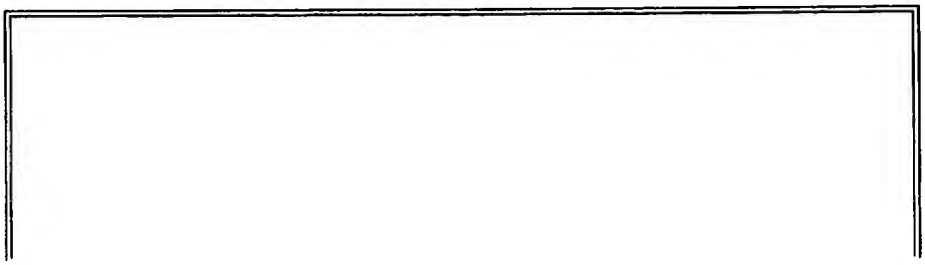
Cytotec should not be used for reducing the risk of NSAID-induced ulcers in women of childbearing potential unless the patient is at high risk of complications from gastric ulcers associated with use of the NSAID, or is at high risk of developing gastric ulceration. In such patients, Cytotec may be prescribed if the patient

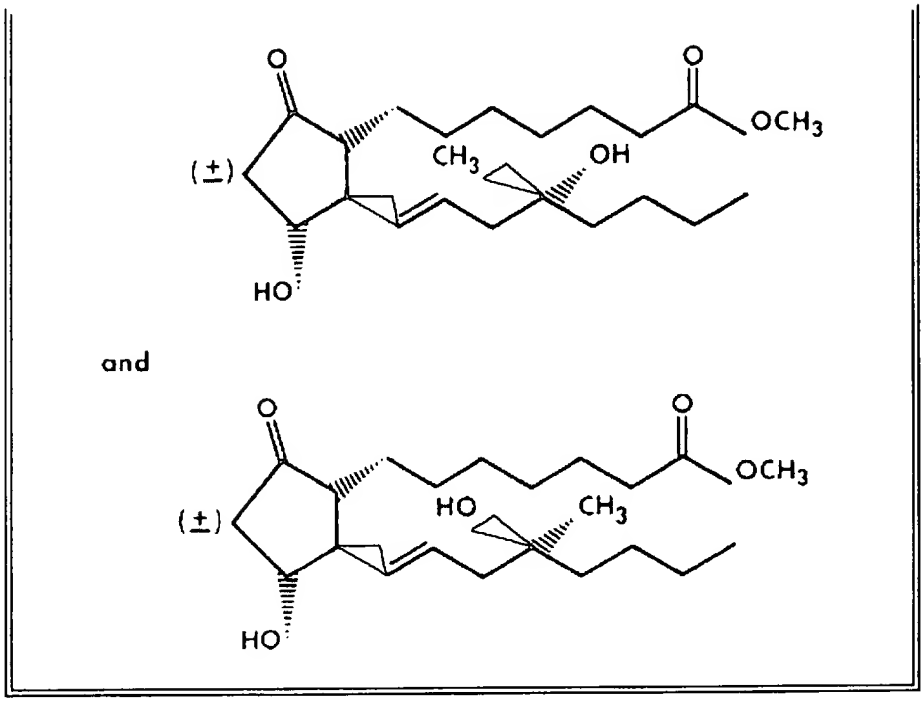
- has had a negative serum pregnancy test within 2 weeks prior to beginning therapy.
- is capable of complying with effective contraceptive measures.
- has received both oral and written warnings of the hazards of misoprostol, the risk of possible contraception failure, and the danger to other women of childbearing potential should the drug be taken by mistake.
- will begin Cytotec only on the second or third day of the next normal menstrual period.

DESCRIPTION

Cytotec oral tablets contain either 100 mcg or 200 mcg of misoprostol, a synthetic prostaglandin E_1 analog.

Misoprostol contains approximately equal amounts of the two diastereomers presented below with their enantiomers indicated by (±):





$C_{22}H_{38}O_5$ M.W. = 382.5

(±) methyl 11(alpha),16-dihydroxy-16-methyl-9-oxoprost-13E-en-1-oate

Misoprostol is a water-soluble, viscous liquid.

Inactive ingredients of tablets are hydrogenated castor oil, hydroxypropyl methylcellulose, microcrystalline cellulose, and sodium starch glycolate.

CLINICAL PHARMACOLOGY

Pharmacokinetics: Misoprostol is extensively absorbed, and undergoes rapid de-esterification to its free acid, which is responsible for its clinical activity and, unlike the parent compound, is detectable in plasma. The alpha side chain undergoes beta oxidation and the beta side chain undergoes omega oxidation followed by reduction of the ketone to give prostaglandin F analogs.

In normal volunteers, Cytotec (misoprostol) is rapidly absorbed after oral administration with a T_{max} of misoprostol acid of 12 ± 3 minutes and a terminal half-life of 20-40 minutes.

There is high variability of plasma levels of misoprostol acid between and within studies but mean values after single doses show a linear relationship with dose over the range of 200-400 mcg. No accumulation of misoprostol acid was noted in multiple dose studies; plasma steady state was achieved within two days.

Maximum plasma concentrations of misoprostol acid are diminished when the dose is taken with food and total availability of misoprostol acid is reduced by use of concomitant antacid. Clinical trials were conducted with concomitant antacid, however, so this effect does not appear to be clinically important.

		AUC(0-4)	
Mean ± SD	**C_{max} (pg/ml)**	**(pg•hr/ml)**	**T_{max} (min)**
Fasting	811 ± 317	417 ± 135	14 ± 8
With Antacid	689 ± 315	349 ± 108 *	20 ± 14
With High Fat Breakfast	303 ± 176 *	373 ± 111	64 ± 79 *
*Comparisons with fasting results statistically significant, $p<0.05$.			

After oral administration of radiolabeled misoprostol, about 80% of detected radioactivity appears in urine. Pharmacokinetic studies in patients with varying degrees of renal impairment showed an approximate doubling of $T_{1/2}$, C_{max}, and AUC compared to normals, but no clear correlation between the degree of impairment and AUC. In subjects over 64 years of age, the AUC for misoprostol acid is increased. No routine dosage adjustment is recommended in older patients or patients with renal impairment, but dosage may need to be reduced if the usual dose is not tolerated.

Cytotec does not affect the hepatic mixed function oxidase (cytochrome P-450) enzyme systems in animals.

Drug interaction studies between misoprostol and several nonsteroidal anti-inflammatory drugs showed no effect on the kinetics of ibuprofen or diclofenac, and a 20% decrease in aspirin AUC, not thought to be clinically significant.

Pharmacokinetic studies also showed a lack of drug interaction with antipyrine and propranolol when these drugs were given with misoprostol. Misoprostol given for 1 week had no effect on the steady state pharmacokinetics of diazepam when the two drugs were administered 2 hours apart.

The serum protein binding of misoprostol acid is less than 90% and is concentration-independent in the therapeutic range.

Pharmacodynamics: Misoprostol has both anti-secretory (inhibiting gastric acid secretion) and (in animals) mucosal protective properties. NSAIDs inhibit prostaglandin synthesis, and a deficiency of prostaglandins within the gastric mucosa may lead to diminishing bicarbonate and mucus secretion and may contribute to the mucosal damage caused by these agents. Misoprostol can increase bicarbonate and mucus production, but in man this has been shown at doses 200 mcg and above that are also antisecretory. It is therefore not possible to tell whether the ability of misoprostol to reduce the risk of gastric ulcer is the result of its antisecretory effect, its mucosal protective effect, or both.

In vitro studies on canine parietal cells using tritiated misoprostol acid as the ligand have led to the identification and characterization of specific prostaglandin receptors. Receptor binding is saturable, reversible, and stereospecific. The sites have a high affinity for misoprostol, for its acid metabolite, and for other E type prostaglandins, but not for F or I prostaglandins and other unrelated compounds, such as histamine or cimetidine. Receptor-site affinity for misoprostol correlates well with an indirect index of antisecretory activity. It is likely that these specific receptors allow misoprostol taken with food to be effective topically, despite the lower serum concentrations attained.

Misoprostol produces a moderate decrease in pepsin concentration during basal conditions, but not during histamine stimulation. It has no significant effect on fasting or postprandial gastrin nor on intrinsic factor output.

Effects on gastric acid secretion: Misoprostol, over the range of 50-200 mcg, inhibits basal and nocturnal gastric acid secretion, and acid secretion in response to a variety of stimuli, including meals, histamine, pentagastrin, and coffee. Activity is apparent 30 minutes after oral administration and persists for at least 3 hours. In general, the effects of 50 mcg were modest and shorter lived, and only the 200-mcg dose had substantial effects on nocturnal secretion or on histamine and meal-stimulated secretion.

Uterine effects: Cytotec has been shown to produce uterine contractions that may endanger pregnancy. (See boxed **WARNINGS** .)

Other pharmacologic effects: Cytotec does not produce clinically significant effects on serum levels of prolactin, gonadotropins, thyroid-stimulating hormone, growth hormone, thyroxine, cortisol, gastrointestinal hormones (somatostatin, gastrin, vasoactive intestinal polypeptide, and motilin), creatinine, or uric acid. Gastric emptying, immunologic competence, platelet aggregation, pulmonary function, or the cardiovascular system are not modified by recommended doses of Cytotec.

Clinical studies: In a series of small short-term (about 1 week) placebo-controlled studies in healthy human volunteers, doses of misoprostol were evaluated for their ability to reduce the risk of NSAID-induced mucosal injury. Studies of 200 mcg q.i.d. of misoprostol with tolmetin and naproxen, and of 100 and 200 mcg q.i.d. with ibuprofen, all showed reduction of the rate of significant endoscopic injury from about 70-75% on placebo to 10-30% on misoprostol. Doses of 25-200 mcg q.i.d. reduced aspirin-induced mucosal injury and bleeding.

Reducing the risk of gastric ulcers caused by nonsteroidal anti-inflammatory drugs (NSAIDs): Two 12-week, randomized, doubleblind trials in osteoarthritic patients who had gastrointestinal symptoms but no ulcer on endoscopy while taking an NSAID compared the ability of 200 mcg of Cytotec, 100 mcg of Cytotec, and placebo to reduce the risk of gastric ulcer (GU) formation. Patients were approximately equally divided between ibuprofen, piroxicam, and naproxen, and continued this treatment throughout the 12 weeks. The 200-mcg dose caused a marked, statistically significant reduction in gastric ulcers in both studies. The lower dose was somewhat less effective, with a significant result in only one of the studies.

Reduction of Risk of Gastric Ulcers Induced by Ibuprofen, Piroxicam, or Naproxen
[No. of patients with ulcer(s) (%)]

	Therapy Duration			
Therapy	**4 weeks**	**8 weeks**	**12 weeks**	
Study No. 1				
Cytotec 200 mcg q.i.d. (n=74)	1 (1.4)	0	0	1 (1.4) *
Cytotec 100 mcg q.i.d. (n=77)	3 (3.9)	1 (1.3)	1 (1.3)	5 (6.5) *
Placebo (n=76)	11 (14.5)	4 (5.3)	4 (5.3)	19 (25.0)
Study No. 2				
Cytotec 200 mcg q.i.d. (n=65)	1 (1.5)	1 (1.5)	0	2 (3.1) *
Cytotec 100 mcg q.i.d. (n=66)	2 (3.0)	2 (3.0)	1 (1.5)	5 (7.6)

Placebo (n=62)	6 (9.7)	2 (3.2)	3 (4.8)	11 (17.7)
Studies No. 1 & No. 2 **				
Cytotec 200 mcg q.i.d. (n=139)	2 (1.4)	1 (0.7)	0	3 (2.2) *
Cytotec 100 mcg q.i.d. (n=143)	5 (3.5)	3 (2.1)	2 (1.4)	10 (7.0) *
Placebo (n=138)	17 (12.3)	6 (4.3)	7 (5.1)	30 (21.7)
* Statistically significantly different from placebo at the 5% level.				
** Combined data from Study No. 1 and Study No. 2.				

In these trials there were no significant differences between Cytotec and placebo in relief of day or night abdominal pain. No effect of Cytotec in reducing the risk of duodenal ulcers was demonstrated, but relatively few duodenal lesions were seen.

In another clinical trial, 239 patients receiving aspirin 650-1300 mg q.i.d. for rheumatoid arthritis who had endoscopic evidence of duodenal and/or gastric inflammation were randomized to misoprostol 200 mcg q.i.d. or placebo for 8 weeks while continuing to receive aspirin. The study evaluated the possible interference of Cytotec on the efficacy of aspirin in these patients with rheumatoid arthritis by analyzing joint tenderness, joint swelling, physician's clinical assessment, patient's assessment, change in ARA classification, change in handgrip strength, change in duration of morning stiffness, patient's assessment of pain at rest, movement, interference with daily activity, and ESR. Cytotec did not interfere with the efficacy of aspirin in these patients with rheumatoid arthritis.

INDICATIONS AND USAGE

Cytotec (misoprostol) is indicated for reducing the risk of NSAID (nonsteroidal anti-inflammatory drugs, including aspirin)-induced gastric ulcers in patients at high risk of complications from gastric ulcer, eg, the elderly and patients with concomitant debilitating disease, as well as patients at high risk of developing gastric ulceration, such as patients with a history of ulcer. Cytotec has not been shown to reduce the risk of duodenal ulcers in patients taking NSAIDs. Cytotec should be taken for the duration of NSAID therapy. Cytotec has been shown to reduce the risk of gastric ulcers in controlled studies of 3 months' duration. It had no effect, compared to placebo, on gastrointestinal pain or discomfort associated with NSAID use.

CONTRAINDICATIONS

See boxed **WARNINGS** .

Cytotec should not be taken by pregnant women to reduce the risk of ulcers induced by nonsteroidal anti-inflammatory drugs (NSAIDs).

Cytotec should not be taken by anyone with a history of allergy to prostaglandins.

WARNINGS

See boxed **WARNINGS** .

PRECAUTIONS

Information for patients: Women of childbearing potential using Cytotec to decrease the risk of NSAID-induced ulcers should be told that they must not be pregnant when Cytotec therapy is initiated, and that they must use an effective contraception method while taking Cytotec.

See boxed **WARNINGS** .

Cytotec is intended for administration along with nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin, to decrease the chance of developing an NSAID-induced gastric ulcer.

Cytotec should be taken only according to the directions given by a physician.

If the patient has questions about or problems with Cytotec, the physician should be contacted promptly.

THE PATIENT SHOULD NOT GIVE CYTOTEC TO ANYONE ELSE. Cytotec has been prescribed for the patient's specific condition, may not be the correct treatment for another person, and may be dangerous to the other person if she were to become pregnant.

The Cytotec package the patient receives from the pharmacist will include a leaflet containing patient information. The patient should read the leaflet before taking Cytotec and each time the prescription is renewed because the leaflet may have been revised.

Keep Cytotec out of the reach of children.

SPECIAL NOTE FOR WOMEN: Cytotec may cause abortion (sometimes incomplete), premature labor, or birth defects if given to pregnant women.

Cytotec is available only as a unit-of-use package that includes a leaflet containing patient information. See *Patient Information* at the end of this labeling.

Drug interactions: See *Clinical Pharmacology* . Cytotec has not been shown to interfere with the beneficial effects of aspirin on signs and symptoms of rheumatoid arthritis. Cytotec does not exert clinically significant effects on the absorption, blood levels, and antiplatelet effects of therapeutic doses of aspirin. Cytotec has no clinically significant effect on the kinetics of diclofenac or ibuprofen.

Animal toxicology: A reversible increase in the number of normal surface gastric epithelial cells occurred in the dog, rat, and mouse. No such increase has been observed in humans administered Cytotec for up to 1 year.

An apparent response of the female mouse to Cytotec in long-term studies at 100 to 1000 times the human dose was hyperostosis, mainly of the medulla of sternebrae. Hyperostosis did not occur in long-term studies in the dog and rat and has not been seen in humans treated with Cytotec.

Carcinogenesis, mutagenesis, impairment of fertility: There was no evidence of an effect of Cytotec on tumor occurrence or incidence in rats receiving daily doses up to 150 times the human dose for 24 months. Similarly, there was no effect of Cytotec on tumor occurrence or incidence in mice receiving daily doses up to 1000 times the human dose for 21 months. The mutagenic potential of Cytotec was tested in several *in vitro* assays, all of which were negative.

Misoprostol, when administered to breeding male and female rats at doses 6.25 times to 625 times the maximum recommended human therapeutic dose, produced dose-related pre- and post-implantation losses and a significant decrease in the number of live pups born at the highest dose. These findings suggest the possibility of a general adverse effect on fertility in males and females.

Pregnancy: Pregnancy Category X.

Teratogenic effects: See boxed **WARNINGS** . Congenital anomalies sometimes associated with fetal death have been reported subsequent to the unsuccessful use of misoprostol as an abortifacient, but the drug's teratogenic mechanism has not been demonstrated. Several reports in the literature associate the use of misoprostol during the first trimester of pregnancy with skull defects, cranial nerve palsies, facial malformations, and limb defects.

Cytotec is not fetotoxic or teratogenic in rats and rabbits at doses 625 and 63 times the human dose, respectively.

Nonteratogenic effects: See boxed **WARNINGS** . Cytotec may endanger pregnancy (may cause abortion) and thereby cause harm to the fetus when administered to a pregnant woman. Cytotec may produce uterine contractions, uterine bleeding, and expulsion of the products of conception. Abortions caused by Cytotec may be incomplete. If a woman is or becomes pregnant while taking this drug to reduce the risk of NSAID-induced ulcers, the drug should be discontinued and the patient apprised of the potential hazard to the fetus.

Labor and delivery: Cytotec can induce or augment uterine contractions. Vaginal administration of Cytotec, outside of its approved indication, has been used as a cervical ripening agent, for the induction of labor and for treatment of serious postpartum hemorrhage in the presence of uterine atony. A major adverse effect of the obstetrical use of Cytotec is the hyperstimulation of the uterus which may progress to uterine tetany with marked impairment of uteroplacental blood flow, uterine rupture (requiring surgical repair, hysterectomy, and/or salpingo-oophorectomy), or amniotic fluid embolism. Pelvic pain, retained placenta, severe genital bleeding, shock, fetal bradycardia, and fetal and maternal death have been reported.

There may be an increased risk of uterine tachysystole, uterine rupture, meconium passage, meconium staining of amniotic fluid, and Cesarean delivery due to uterine hyperstimulation with the use of higher doses of Cytotec, including the manufactured 100 mcg tablet. The risk of uterine rupture increases with advancing gestational ages and with prior uterine surgery, including Cesarean delivery. Grand multiparity also appears to be a risk factor for uterine rupture.

The effect of Cytotec on later growth, development, and functional maturation of the child when Cytotec is used for cervical ripening or induction of labor have not been established. Information on Cytotec's effect on the need for forceps delivery or other intervention is unknown.

Nursing mothers: It is unlikely that Cytotec is excreted in human milk since it is rapidly metabolized throughout the body. However, it is not known if the active metabolite (misoprostol acid) is excreted in human milk. Therefore, Cytotec should not be administered to nursing mothers because the potential excretion of misoprostol acid could cause significant diarrhea in nursing infants.

Pediatric use: Safety and effectiveness of Cytotec in pediatric patients have not been established.

ADVERSE REACTIONS

The following have been reported as adverse events in subjects receiving Cytotec:

Gastrointestinal: In subjects receiving Cytotec 400 or 800 mcg daily in clinical trials, the most frequent gastrointestinal adverse events were diarrhea and abdominal pain. The incidence of diarrhea at 800 mcg in controlled trials in patients on NSAIDs ranged from 14-40% and in all

studies (over 5,000 patients) averaged 13%. Abdominal pain occurred in 13-20% of patients in NSAID trials and about 7% in all studies, but there was no consistent difference from placebo.

Diarrhea was dose related and usually developed early in the course of therapy (after 13 days), usually was self-limiting (often resolving after 8 days), but sometimes required discontinuation of Cytotec (2% of the patients). Rare instances of profound diarrhea leading to severe dehydration have been reported. Patients with an underlying condition such as inflammatory bowel disease, or those in whom dehydration, were it to occur, would be dangerous, should be monitored carefully if Cytotec is prescribed. The incidence of diarrhea can be minimized by administering after meals and at bedtime, and by avoiding coadministration of Cytotec with magnesium-containing antacids.

Gynecological: Women who received Cytotec during clinical trials reported the following gynecological disorders: spotting (0.7%), cramps (0.6%), hypermenorrhea (0.5%), menstrual disorder (0.3%) and dysmenorrhea (0.1%). Postmenopausal vaginal bleeding may be related to Cytotec administration. If it occurs, diagnostic workup should be undertaken to rule out gynecological pathology. (See boxed **WARNINGS** .)

Elderly: There were no significant differences in the safety profile of Cytotec in approximately 500 ulcer patients who were 65 years of age or older compared with younger patients.

Additional adverse events which were reported are categorized as follows:

Incidence greater than 1%: In clinical trials, the following adverse reactions were reported by more than 1% of the subjects receiving Cytotec and may be causally related to the drug: nausea (3.2%), flatulence (2.9%), headache (2.4%), dyspepsia (2.0%), vomiting (1.3%), and constipation (1.1%). However, there were no significant differences between the incidences of these events for Cytotec and placebo.

Causal relationship unknown: The following adverse events were infrequently reported. Causal relationships between Cytotec and these events have not been established but cannot be excluded:

Body as a whole: aches/pains, asthenia, fatigue, fever, rigors, weight changes.

Skin: rash, dermatitis, alopecia, pallor, breast pain.

Special senses: abnormal taste, abnormal vision, conjunctivitis, deafness, tinnitus, earache.

Respiratory: upper respiratory tract infection, bronchitis, bronchospasm, dyspnea, pneumonia, epistaxis.

Cardiovascular: chest pain, edema, diaphoresis, hypotension, hypertension, arrhythmia, phlebitis, increased cardiac enzymes, syncope.

Gastrointestinal: GI bleeding, GI inflammation/infection, rectal disorder, abnormal hepatobiliary function, gingivitis, reflux, dysphagia, amylase increase.

Hypersensitivity: anaphylaxis

Metabolic: glycosuria, gout, increased nitrogen, increased alkaline phosphatase.

Genitourinary: polyuria, dysuria, hematuria, urinary tract infection.

Nervous system/Psychiatric: anxiety, change in appetite, depression, drowsiness, dizziness, thirst,

impotence, loss of libido, sweating increase, neuropathy, neurosis, confusion.

Musculoskeletal: arthralgia, myalgia, muscle cramps, stiffness, back pain.

Blood/Coagulation: anemia, abnormal differential, thrombocytopenia, purpura, ESR increased.

OVERDOSAGE

The toxic dose of Cytotec in humans has not been determined. Cumulative total daily doses of 1600 mcg have been tolerated, with only symptoms of gastrointestinal discomfort being reported. In animals, the acute toxic effects are diarrhea, gastrointestinal lesions, focal cardiac necrosis, hepatic necrosis, renal tubular necrosis, testicular atrophy, respiratory difficulties, and depression of the central nervous system. Clinical signs that may indicate an overdose are sedation, tremor, convulsions, dyspnea, abdominal pain, diarrhea, fever, palpitations, hypotension, or bradycardia. Symptoms should be treated with supportive therapy.

It is not known if misoprostol acid is dialyzable. However, because misoprostol is metabolized like a fatty acid, it is unlikely that dialysis would be appropriate treatment for overdosage.

DOSAGE AND ADMINISTRATION

The recommended adult oral dose of Cytotec for reducing the risk of NSAID-induced gastric ulcers is 200 mcg four times daily with food. If this dose cannot be tolerated, a dose of 100 mcg can be used. (See *Clinical Pharmacology* : *Clinical studies* .) Cytotec should be taken for the duration of NSAID therapy as prescribed by the physician. Cytotec should be taken with a meal, and the last dose of the day should be at bedtime.

Renal impairment: Adjustment of the dosing schedule in renally impaired patients is not routinely needed, but dosage can be reduced if the 200-mcg dose is not tolerated. (See *Clinical Pharmacology* .)

HOW SUPPLIED

Cytotec 100-mcg tablets are white, round, with SEARLE debossed on one side and 1451 on the other side; supplied as:

NDC Number	Size
0025-1451-60	unit-of-use bottle of 60
0025-1451-20	unit-of-use bottle of 120
0025-1451-34	carton of 100 unit dose

Cytotec 200-mcg tablets are white, hexagonal, with SEARLE debossed above and 1461 debossed below the line on one side and a double stomach debossed on the other side; supplied as:

NDC Number	Size
0025-1461-60	unit-of-use bottle of 60
0025-1461-31	unit-of-use bottle of 100

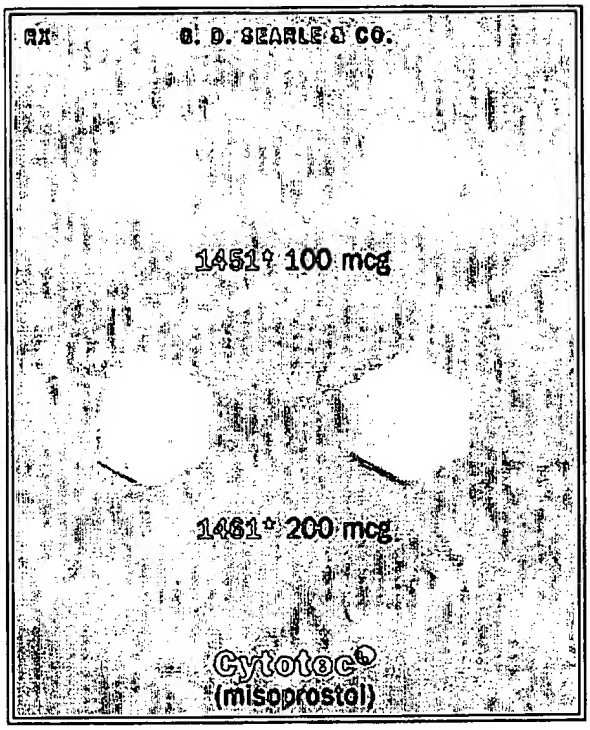
0025-1461-34 carton of 100 unit dose

Store at or below 25°C (77°F), in a dry area.

PRODUCT PHOTO(S):

NOTE: These photos can be used only for identification by shape, color, and imprint. They do not depict actual *or relative* size.

The product samples shown here have been supplied by the manufacturer and reproduced in full color by PDR as a quick-reference identification aid. While every effort has been made to assure accurate reproduction, please remember that any visual identification should be considered preliminary. In cases of poisoning or suspected overdosage, the drug's identity should be verified by chemical analysis.



PATIENT INFORMATION

Read this leaflet before taking Cytotec® (misoprostol) and each time your prescription is renewed, because the leaflet may be changed.

Cytotec (misoprostol) is being prescribed by your doctor to decrease the chance of getting stomach ulcers related to the arthritis/pain medication that you take.

Do not take Cytotec to reduce the risk of NSAID-induced ulcers if you are pregnant. (See boxed **WARNINGS** .) Cytotec can cause abortion (sometimes incomplete which could lead to dangerous bleeding and require hospitalization and surgery), premature birth, or birth defects. It is also important to avoid pregnancy while taking this medication and for at least one month or through one menstrual cycle after you stop taking it. Cytotec has been reported to cause the uterus to rupture (tear) when given after the eighth week of pregnancy. Rupture (tearing) of the uterus can

result in severe bleeding, hysterectomy, and/or maternal or fetal death.

If you become pregnant during Cytotec therapy, stop taking Cytotec and contact your physician immediately. Remember that even if you are on a means of birth control it is still possible to become pregnant. Should this occur, stop taking Cytotec and contact your physician immediately.

Cytotec may cause diarrhea, abdominal cramping, and/or nausea in some people. In most cases these problems develop during the first few weeks of therapy and stop after about a week. You can minimize possible diarrhea by making sure you take Cytotec with food.

Because these side effects are usually mild to moderate and usually go away in a matter of days, most patients can continue to take Cytotec. If you have prolonged difficulty (more than 8 days), or if you have severe diarrhea, cramping and/or nausea, call your doctor.

Take Cytotec only according to the directions given by your physician.

Do not give Cytotec to anyone else. It has been prescribed for your specific condition, may not be the correct treatment for another person, and would be dangerous if the other person were pregnant.

This information sheet does not cover all possible side effects of Cytotec. This patient information leaflet does not address the side effects of your arthritis/pain medication. See your doctor if you have questions.

Keep out of reach of children.

Rx only Revised: March 2002

Manufactured for:

G.D. Searle LLC

A subsidiary of Pharmacia Corporation

Chicago, IL 60680, USA

by:

Pharmacia Limited *Searle & Co.*

Morpeth, England *Caguas, PR*

818 931 001 P04011-1

This is Exhibit F referred to in the Declaration of Dr. Michael M. Lipp, sworn this 12th day of November, 2003

A Commissioner, Notary Public
for taking oaths

CINDY A. SRAGG
Notary Public
My Commission Expires
January 23, 2009

Pharmaceutics: The Science of Dosage Form Design

EDITED BY

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EDINBURGH LONDON MELBOURNE AND NEW YORK 1988

37

M P Summers

Granulation

INTRODUCTION TO GRANULATION

Granulation is the process in which powder particles are made to adhere to form larger particles called granules. In the majority of cases this will be undertaken in the production of tablets or capsules, when granules will be made as an intermediate product, but granules may also be used as a dosage form (see Chapter 17). Granulation will commence after mixing the necessary powdered ingredients so that a uniform distribution of each ingredient through the mix is achieved. After granulation, the granules will be packed when used as a dosage form or they may be mixed with other excipients prior to tablet compression or capsule filling.

Reasons for granulation

The reasons why granulation is often necessary are as follows.

To prevent segregation of the constituents in the powder mix

Segregation is primarily due to differences in the size or density of the components, the smaller particles concentrating at the base of a container with the large particles above them. An ideal granulation will contain all the constituents of the mix

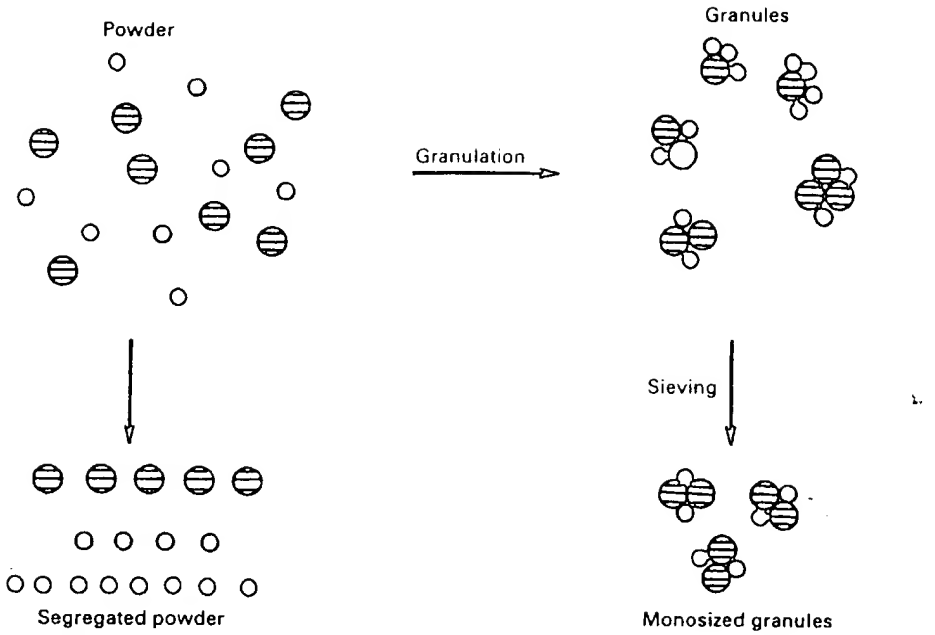

Fig. 37.1 Granulation to prevent powder segregation

in each granule and segregation of the ingredients will not occur (Fig. 37.1).

It is also important to control the particle size distribution of the granules because, although the individual components may not segregate, if there is a wide size distribution, the granules themselves may segregate. If this occurs in the hoppers of sachet filling machines, capsule filling machines or tablet machines, products having large weight variations will result. This is because these machines fill by volume rather than weight and if different regions in the hopper contain granules of different sizes (and hence bulk density), a given volume in each region will contain a different weight of granules. This will lead to an unacceptable distribution of the drug content within the batch of finished product even though the drug is evenly distributed weight per weight, through the granules.

To improve the flow properties of the mix

Many powders, because of their small size or surface characteristics, are cohesive and do not flow well. Poor flow will often result in a wide weight variation within the final product due to variable fill of tablet dies, etc. Granules produced from such a cohesive system will be larger and more isodiametric, both factors contributing to improved flow properties.

To improve the compression characteristics of the mix

Some powders are difficult to compress even if a readily compressed adhesive is included in the mix but granules of the same formulation are often more easily compressed and produce stronger tablets. This is associated with the distribution of the adhesive within the granule and is a function of the method employed to produce the granule (Seager *et al.*, 1979).

Other reasons

These are the primary reasons for the granulation of pharmaceutical products but there are other reasons which may necessitate the granulation of powdered material:

1 The granulation of toxic materials will reduce

the hazard of the generation of toxic dust which may arise when handling powders. Suitable precautions must be taken to ensure that such dust is not a hazard during the granulation process.

2 Materials which are slightly hygroscopic may adhere and form a cake if stored as a powder. Granulation may reduce this hazard as the granules will be able to absorb some moisture and yet retain their flowability because of their size.

3 Granules, being denser than the parent powder mix, occupy less volume per unit weight. They are therefore more convenient for storage or shipment.

Methods of granulation

Granulation methods can be divided into two types: wet methods which utilize a liquid in the process and dry methods in which no liquid is used.

In a suitable formulation a number of different excipients will be needed in addition to the drug. The common types used are diluents, to produce a unit dose weight of suitable size and disintegrating agents which are added to disintegrate the granule in a liquid medium, e.g. on ingestion by the patient. Adhesives in the form of a dry powder may also be added, particularly if dry granulation is employed. These ingredients will be mixed before granulation.

Dry granulation

In the dry methods of granulation the powder particles are aggregated using high pressure. There are two main processes. Either a large tablet (known as a 'slug') is produced in a heavy duty tableting press (a process known as 'slugging') or squeezed between two rollers to produce a sheet of material ('roller compaction'). In both cases these are broken using a suitable milling technique to produce granular material which is usually sieved to separate the desired size fraction. The unused fine material may be recycled to avoid waste. This dry method may be used for drugs which do not compress well after wet granulation or those which are sensitive to moisture.

Wet granulation (or wet massing)

Wet granulation involves the massing of the powder mix using a solvent. The solvents used must be volatile, so that they can be removed by drying, and non-toxic. Typical solvents include water, ethanol and isopropanol either alone or in combination. The solvent may be used alone or it may contain a dissolved adhesive (also referred to as binder or binding agent) which is used to cause particle adhesion. The disadvantages of water as a solvent are that it may adversely affect drug stability, causing hydrolysis of susceptible products and it needs a longer drying time than organic solvents. This long drying time increases the length of the process and again may affect stability because of the extended exposure to heat. The primary advantage of water is that it is non-flammable which means that expensive safety precautions such as the use of flame-proof equipment need not be taken. Organic solvents are used when water-sensitive drugs are processed, as an alternative to dry granulation, or when a rapid drying time is required.

In the traditional wet granulation method the wet mass is forced through a sieve to produce wet granules which are then dried. A subsequent sieving stage breaks agglomerates of granules and removes the fine material which can be recycled. Variations of this traditional method are dependent upon the equipment used but the general principle of initial particle adhesion using a liquid remains in all of the processes.

Effect of granulation method on granule structure

The type and capacity of granulating mixers significantly influences the work input and time necessary to produce a cohesive mass, adequate liquid distribution and intragranular porosity of the granular mass. The method and conditions of granulation affect intergranular and intragranular pore structure by changing the degree of packing within the granules. Seager *et al.* (1979) investigated the structure of granules prepared by various granulation methods. They showed that precompressed granules, consisting of compressed drug and binder particles, were held together by simple bonding during compaction. Granules

prepared by the wet massing consisted of intact drug particles held together in a sponge-like matrix of binder. Fluidized bed granules were similar to granules prepared by the wet massing process, but possessed greater porosity, and the granule surface was covered by a film of binding agent. With spray-dried systems, the granules consisted of spherical particles composed of an outer shell with an inner core of particles. This study graphically indicates that the properties of the granule are influenced by the manufacturing process.

PARTICLE BONDING MECHANISMS

To form granules, bonds must be formed between powder particles so that they adhere and these bonds must be sufficiently strong to prevent breakdown of the granule to powder in subsequent handling operations.

Rumpf (1962) distinguished five primary bonding mechanisms between particles:

1 adhesion and cohesion forces in immobile liquid films,
2 interfacial forces in mobile liquid films,
3 solid bridges,
4 attractive forces between solid particles,
5 interlocking bonds.

Different types of mechanism were identified in each group and the ones discussed below are those which are of relevance to pharmaceutical granulations.

Adhesion and cohesion forces in immobile films

If sufficient liquid is present in a powder to form a very thin, immobile layer, there will be an effective decrease in interparticulate distance and increase in contact area between the particles. The bond strength between the particles will be increased because of this, as the van der Waals forces of attraction are proportional to the particle diameter and inversely proportional to the square of the distance of separation.

This situation will arise with adsorbed moisture and accounts for the cohesion of slightly damp powders. Although such films may be present as residual liquid after granules prepared by wet granulation have been dried, it is unlikely that they contribute significantly to the final granule strength. In dry granulation, however, the pressures used will increase the contact area between the adsorption layers and decrease the interparticulate distance and this will contribute to the final granule strength.

Thin, immobile layers may also be formed by highly viscous solutions of adhesives and so the bond strength will be greater than that produced by the mobile films discussed below. The use of starch mucilage in pharmaceutical granulations may produce this type of film.

Interfacial forces in mobile liquid films

During wet granulation liquid is added to the powder mix and will be distributed as films around and between the particles. Sufficient liquid is usually added to exceed that necessary for an immobile layer and produce a mobile film. Newitt and Conway-Jones (1958) distinguished three states of water distribution between particles which are illustrated in Fig. 37.2.

At low moisture levels, termed the pendular state, the particles are held together by lens-

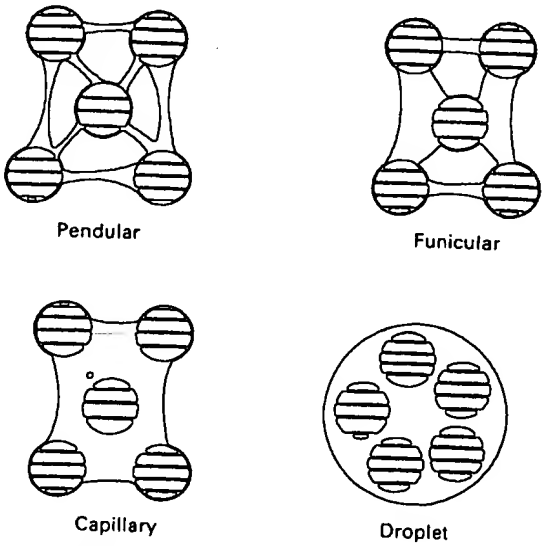

Fig. 37.2 Water distribution between particles

shaped rings of liquid. These cause adhesion because of the surface tension forces of the liquid–air interface and the hydrostatic suction pressure in the liquid bridge. When all the air has been displaced from between the particles the capillary stage is reached and the particles are held by capillary suction at the liquid–air interface which is now only at the granule surface. The funicular state represents an intermediate stage between the pendular and capillary states. Moist-granule tensile strength increases about three times from the pendular to capillary state.

It may appear that the state of the powder bed is dependent upon the total moisture content of the wetted powders but the capillary state may also be reached by decreasing the separation of the particles. In the massing process during wet granulation, continued kneading/mixing of material originally in the pendular state will densify the wet mass, decreasing the pore volume occupied by air and eventually producing the funicular or capillary state without further liquid addition.

In addition to these three states, a further state, the droplet, is illustrated in Fig. 37.2. This will be important in the process of granulation by spray drying of a suspension. In this state, the strength of the droplet is dependent upon the surface tension of the liquid used.

These wet bridges are only temporary structures in wet granulation because the moist granules will be dried. They are, however, a prerequisite for the formation of solid bridges formed by adhesives present in the liquid or by materials which dissolve in the granulating liquid.

Solid bridges

These can be formed by:

1 partial melting,
2 hardening binders,
3 crystallization of dissolved substances.

Partial melting

Although not considered to be a predominant mechanism in pharmaceutical materials, it is possible that the pressures used in dry granulation methods may cause melting of low melting point materials where the particles touch and high pressures are developed. When the pressure is relieved, crystallization will take place and bind the particles together.

Hardening binders

This is the common mechanism in pharmaceutical wet granulations when an adhesive is included in the granulating solvent. The liquid will form liquid bridges, as discussed above, and the adhesive will harden or crystallize on drying to form solid bridges to bind the particles. Adhesives such as polyvinylpyrrolidone, the cellulose derivatives (such as carboxymethylcellulose) and starch (added as a mucilage) all function in this way.

Crystallization of dissolved substances

The solvent used to mass the powder during wet granulation may dissolve one of the powdered ingredients. When the granules are dried, crystallization of this material will take place and the dissolved substance then acts as a hardening binder. Any material soluble in the granulating liquid will function in this manner; e.g. sucrose incorporated into dry powders granulated with water.

The size of the crystals produced in the bridge will be influenced by the rate of drying of the granules; the slower the drying time, the larger the particle size. It is therefore important that the drug does not dissolve in the granulating liquid and recrystallize because it may adversely affect the dissolution rate of the drug if crystals larger than that of the starting material are produced.

Attractive forces between solid particles

In the absence of liquids and solid bridges formed by binding agents, there are two types of attractive force which can operate between particles in pharmaceutical systems.

Electrostatic forces may be of importance in causing powder cohesion and the initial formation of agglomerates, e.g. during mixing. In general they do not contribute significantly to the final strength of the granule.

Van der Waals forces, however, are about four

orders of magnitude greater than electrostatic forces and contribute significantly to the strength of granules produced by dry granulation. The magnitude of these forces will increase as the distance between adjacent surfaces decreases and in dry granulation this is achieved using pressure to force the particles together.

MECHANISMS OF GRANULE FORMATION

In the dry methods, adhesion of particles takes place because of applied pressure. A compact or sheet is produced which is larger than the granule size required and therefore the required size can be attained by milling and sieving.

In wet granulation methods, liquid added to dry powders has to be distributed through the powder by the mechanical agitation produced in the granulator. The particles adhere to each other because of liquid films and further agitation and/or liquid addition causes more particles to adhere. The precise mechanism by which a dry powder is transformed into a bed of granules is probably different for each type of granulation equipment but the mechanism discussed below, originally proposed for pan granulators, serves as a useful broad generalization of the process. The Freund granulator discussed later in this chapter utilizes a principle similar to that of a pan granulator and the mechanism will therefore be of direct relevance to granulation in this type of equipment.

The proposed granulation mechanism can be divided into three stages (Barlow, 1968):

Nucleation

Granulation starts with particle–particle contact and adhesion due to liquid bridges. A number of particles will join to form the pendular state illustrated in Fig. 37.2. Further agitation densifies the pendular bodies to form the capillary state and these bodies act as nuclei for further granule growth.

Transition

Nuclei can grow by two possible mechanisms: either single particles can be added to the nuclei by pendular bridges or two or more nuclei may combine. The combined nuclei will be reshaped by the agitation of the bed.

This stage is characterized by the presence of a large number of small granules with a fairly wide size distribution. Providing that the size distribution is not excessively large, this point represents a suitable end-point for granules used in capsule and tablet manufacture as relatively small granules will produce a uniform tablet die or capsule fill. Larger granules may give rise to problems in small diameter dies due to bridging across the die and uneven fill.

Ball growth

Further granule growth produces large, spherical granules and the mean particle size of the granulating system will increase with time. If agitation is continued, granule coalescence will continue and produce an unusable, overmassed system although this is dependent upon the amount of liquid added and the properties of the material being granulated.

Although ball growth produces granules which may be too large for pharmaceutical purposes, some degree of ball growth will occur in planetary mixers and it is an essential feature of some spheronizing equipment.

The four possible mechanisms of ball growth have been summarized by Sastry and Fuerstenau (1973) and are illustrated in Fig. 37.3.

Coalescence

Two or more granules join to form a larger granule.

Breakage

Granules break into fragments which adhere to other granules forming a layer of material over the surviving granule.

Abrasion transfer

Agitation of the granule bed leads to attrition of material from granules. This abraded material adheres to other granules, increasing their size.

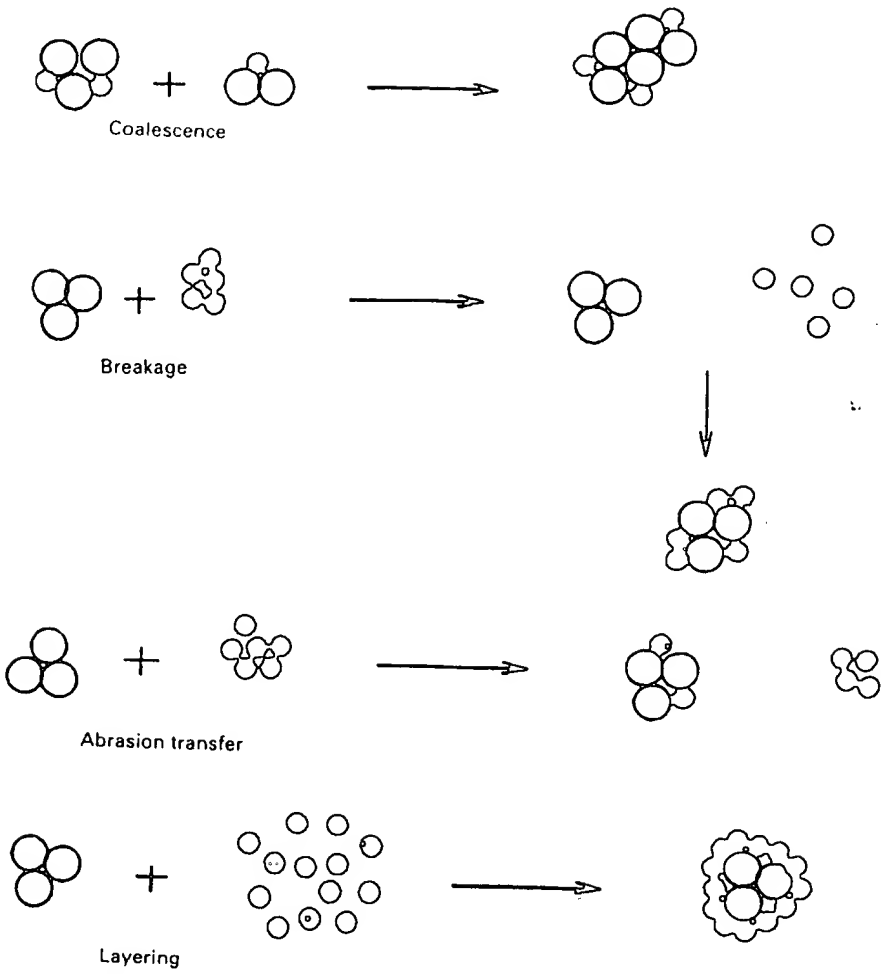

Fig. 37.3 Mechanisms of ball growth during granulation

Layering

When a second batch of powder mix is added to a bed of granules, the powder will adhere to the granules forming a layer over the surface increasing the granule size. This mechanism is only of relevance to the production of layered granules using spheronizing equipment.

There will be some degree of overlap between these stages and it will be very difficult to identify a given stage by inspection of the granulating system. For end-product uniformity it is desirable to finish every batch of a formulation at the same stage and this may be a major problem in pharmaceutical production.

Using the slower processes such as the planetary mixer, there is usually a sufficient length of time to stop the process before overmassing. In faster granulation equipment, the duration of granulation can only be used as a control parameter when the formulation is such that granule growth is slow and takes place at a fairly uniform rate. In many cases, however, the transition from a non-granulated to an overmassed system is very rapid and monitoring equipment is necessary to stop the granulation at a predetermined point. Although

the topic of granulation end-point control is beyond the scope of this chapter, useful references are given in the bibliography.

PHARMACEUTICAL GRANULATION EQUIPMENT

Wet granulators

There are three main types of granulator used within the pharmaceutical industry for wet granulation.

Shear granulators

In the traditional granulation process a planetary mixer is often used for wet massing of the powders, e.g. Hobart, Collette, Beken (Fig. 37.4). Powder mixing usually has to be performed as a separate operation using suitable mixing equipment. With some formulations, such as those containing two or three ingredients in approximately equal quantities, however, it may be possible to achieve a suitable mix in the planetary mixer without a separate stage.

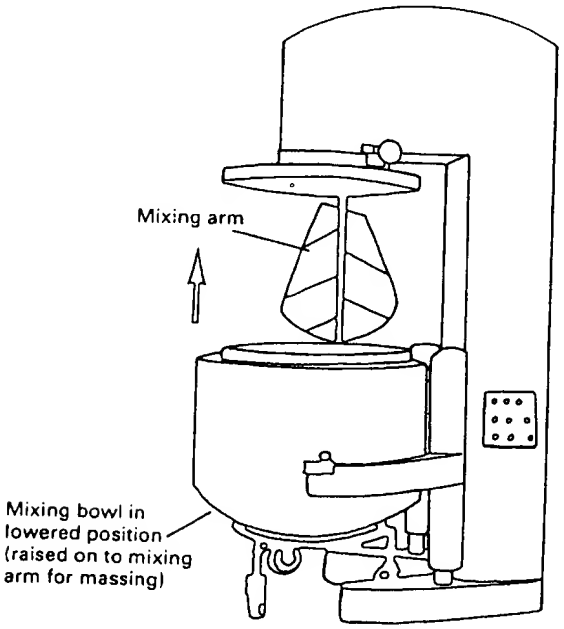

Fig. 37.4 Planetary mixer for wet massing

The mixed powders are fed into the bowl of the planetary mixer and granulating liquid added as the paddle of the mixer agitates the powders. The planetary action of the blade when mixing is similar to that of a household mixer.

The moist mass has then to be transferred to a granulator such as an oscillating granulator (Fig. 37.5). The rotor bars of the granulator oscillate and force the moist mass through the sieve screen, the size of which determines the granule size. The mass should be sufficiently moist to form discrete granules when sieved. If excess liquid is added, strings of material will be formed and if the mix is too dry the mass will be sieved to powder and granules will not be formed. The granules can be collected on trays and transferred to a drying oven although tray drying suffers from three major disadvantages:

1 There is a long drying time.
2 Migration of dissolved material to the upper surface of the bed of granules can take place as the solvent is only removed from the upper surface of the bed on the tray.
3 Granules may aggregate due to bridges formed at the points of contact of the granules.

To deaggregate the granules and remix them, a sieving stage is necessary after drying.

An alternative method is to dry the granules using a fluidized bed drier. This is a quicker method and as it keeps the individual granules separated during drying, it reduces the problems of aggregation and intergranular solute migration, reducing the need for a sieving stage after drying

The disadvantages of this traditional granulation process are its long duration, the need for

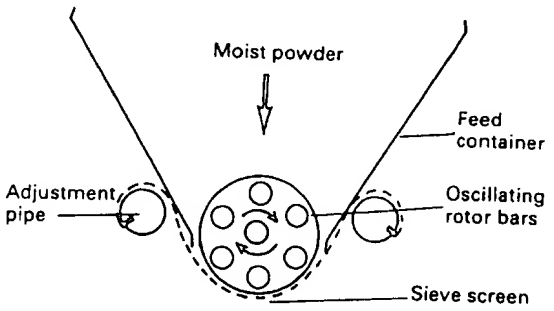

Fig. 37.5 Oscillating granulator

several pieces of equipment and the high material losses which can be incurred because of the transfer stages. Advantages are that the process is not very sensitive to changes in the characteristics of the granule ingredients (e.g. surface area variations in different batches of an excipient) and the end-point of the massing process can often be determined by inspection.

High speed mixer/granulators (e.g. Diosna, Fielder)

This type of granulator was originally designed solely for mixing purposes but is now used extensively for granulation. The machines have a stainless steel mixing bowl containing a three-bladed impeller which revolves in the horizontal plane and a three-bladed auxiliary chopper which revolves in the vertical plane (Fig. 37.6).

The unmixed powders are placed in the bowl and mixed by the rotating impeller. Granulating liquid is then added via a port in the lid and this is mixed into the powders by the impeller. The chopper is usually switched on when the moist mass is formed because its function is to break up the mass to produce a bed of fine, granular material. This granular product is usually sieved as it is being discharged into the bowl of a fluid bed driver simply to remove large aggregates.

The advantage of the process is that mixing, massing and granulation are all performed in a short period in the same piece of equipment. Granulation progresses so rapidly that a usable granule can be transformed very quickly into an unusable, overmassed system and it is often necessary to use a suitable monitoring system to indicate the end of the granulation process, i.e. when a granule of the desired properties has been attained. The process is also sensitive to variations in raw materials but this may be minimized by using a suitable end-point monitor.

A variation of the Diosna/Fielder design is the Collette-Gral mixer (Fig. 37.7). Based on the bowl and overhead drive of the planetary mixer, the single paddle is replaced with two mixing shafts. One of these carries three blades which rotate in the horizontal plane at the base of the bowl and the second carries smaller blades which act as the chopper and rotate in the horizontal plane in the upper regions of the granulating mass.

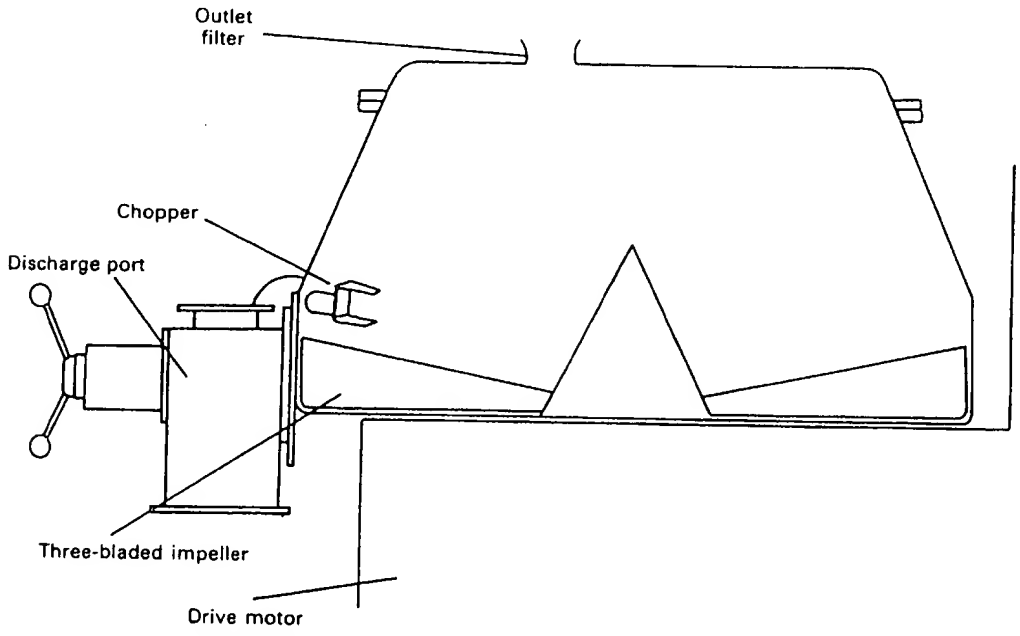

Fig. 37.6 High speed mixer/granulator

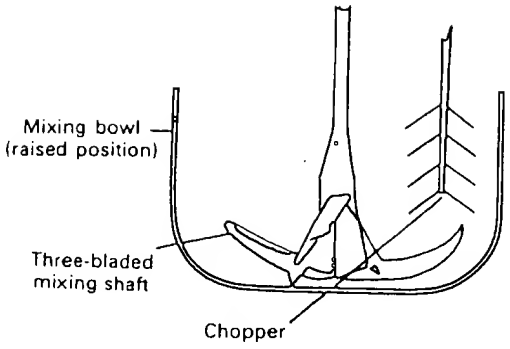

Fig. 37.7 Collette-Gral granulator: mixing shafts and bowl

Fluidized bed granulators (e.g. Aeromatic, Glatt)

The same principle utilized in fluidized bed drying, i.e. the fluidization of powder particles in a stream of air, is utilized for granulation in equipment of this type.

Heated air is blown or sucked through a bed of unmixed powders to fluidize the particles and mix the powders. Granulating liquid is pumped through a spray nozzle over the particles and this liquid causes them to adhere when they collide. Escape of material from the granulation chamber is prevented by exhaust filters which are periodically agitated to reintroduce the collected material into the fluidized bed (Fig. 37.8). Sufficient liquid is added to produce granules of the required size which are then dried in the heated fluidizing air stream.

All the processes which normally need separate equipment in the traditional method are performed in one unit, saving labour costs, transfer losses and time although the equipment is initially expensive. Other advantages of the process are that units are available with in-line condensers for solvent recovery, the production of layered granules is possible and automation of the process can be achieved once the conditions affecting the granulation have been optimized.

The optimization of process (and product) parameters affecting granulation needs extensive development work not only during initial formulation work but also during scale-up from devel-

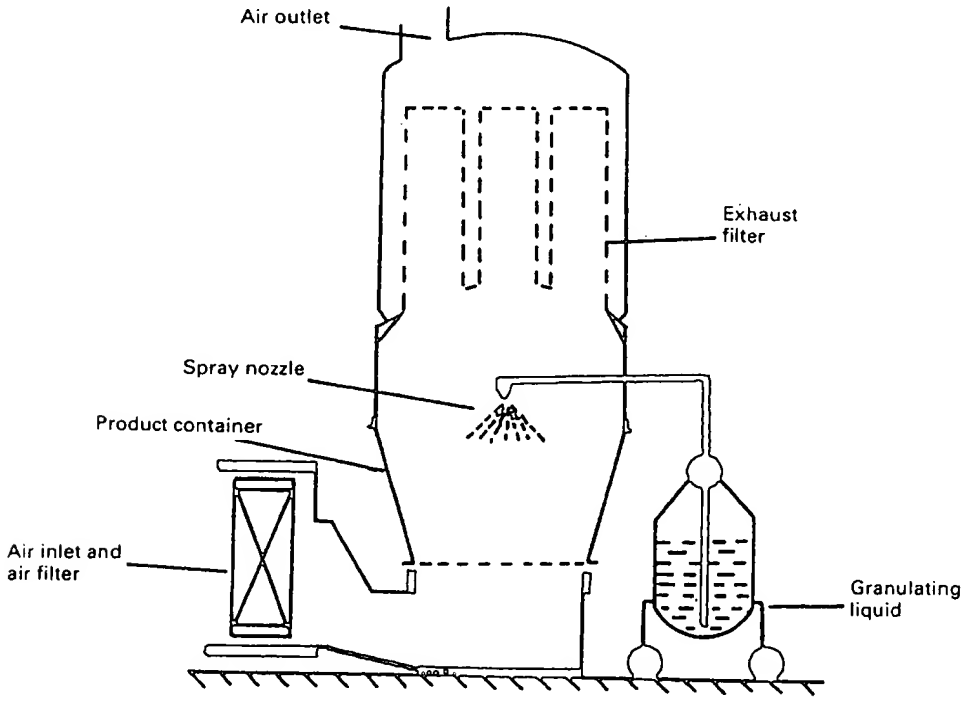

Fig. 37.8 Fluidized bed granulator

opment to production scale. Similar development work for the traditional process and that using high-speed granulators is not as extensive. The parameters affecting the quality of the final granule include such variables as the adhesive concentration used in the granulating solution, the type of adhesive, the velocity and temperature of the fluidizing air and the air pressure used to atomize the granulating liquid. A useful summary of the effects of these variables is given by Aulton and Banks (1978).

The above are the three methods most commonly used in pharmaceutical processes but for more specialized applications other equipment can be utilized.

Spray driers

A suspension of drug and excipients in adhesive solution can be dried in a spray drier (see Chapter 38). The resultant granules are free-flowing hollow spheres and the distribution of adhesive in such granules results in good compression properties (Seager *et al.*, 1979).

This process can be used to make tablet granules although it is probably economically justified for this purpose only when used almost continuously or when suitable granules cannot be produced by the other methods. The primary advantages of the process are the short drying time and the minimal exposure of the product to heat due to the short residence time in the drying chamber. This means that little deterioration of heat-sensitive materials takes place and it may be the only process suitable for this type of product.

Spheronizers/pelletizers

For some applications it may be desirable to have a dense, spherical pellet of the type difficult to produce with the equipment above, and spheronizing or pelletizing equipment is used, e.g. Caleva Spheroniser, Freund CF Granulator. Such pellets could be used, for example, for capsule filling when coated and non-coated drug-containing pellets would give some degree of programmed drug release after the capsule disintegrates.

In the Freund granulator, the powder mix is added to the bowl and wetted with granulating liquid (Fig. 37.9). The base plate rotates at high speed and centrifugal force keeps the moist mass at the edges of the rotor where the velocity difference between the rotor and static walls causes the mass to roll and break up, forming discrete spherical pellets. These are dried by the heated inlet air from the air chamber which also acts as a positive-pressure seal during granulation.

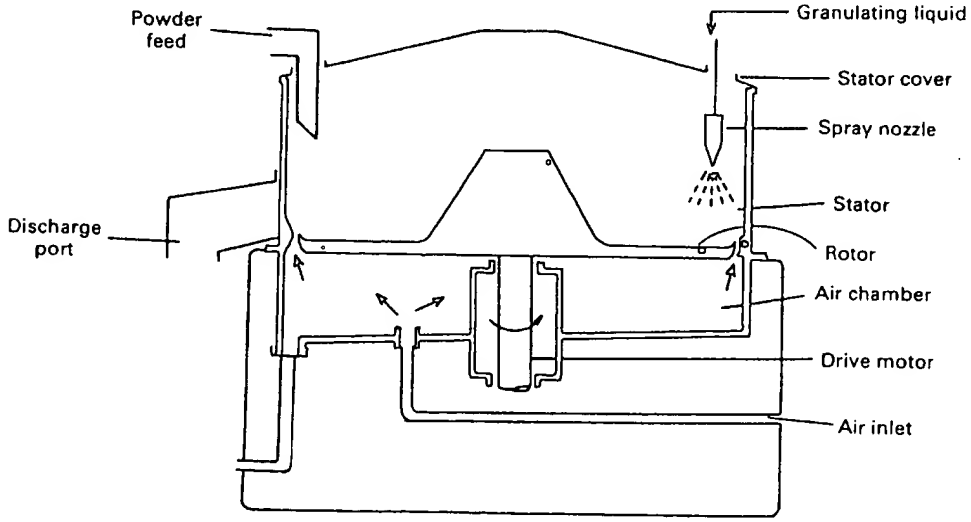

Fig. 37.9 Freund granulator

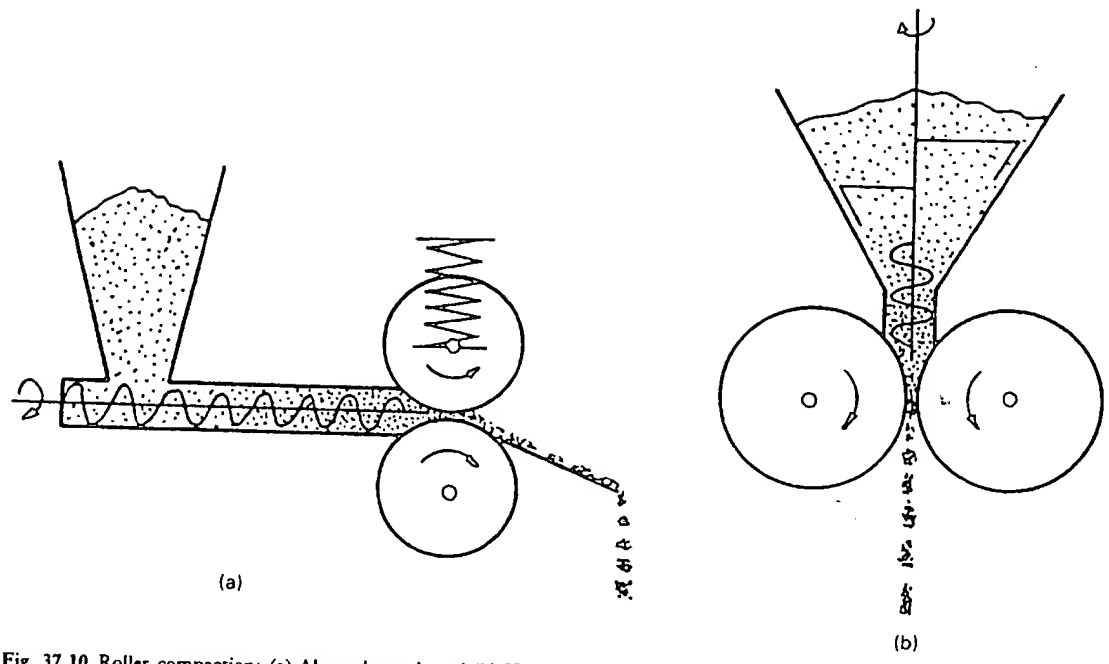

Fig. 37.10 Roller compaction: (a) Alexanderwerk and (b) Hutt types

Using this technique it is possible to coat the pellets by spraying coating solution on to the rotating pellets and layered pellets can be produced by using the pellets as nuclei in a second granulation with a powder mix of the coating ingredients.

The rotating base plate is a common feature of spheronizing equipment but some utilize a feed of pregranulated material which has been massed and extruded into short strings. Extrusion is a similar process to granulation in an oscillating granulator but requires a more moist mass than granulation processes and a more robust screen than that normally used in an oscillating granulator. For extrusion the wet mass can be fed through a perforated plate by an auger feed, a principle similar to that of the household mincer. The strings are fed on to a grooved or smooth rotating base plate and a velocity difference created by having static walls at the edge of the rotating plate breaks the material and rolls it into spheres. The spheres have then to be transferred to a fluidized bed drier for the drying process.

Dry granulators

The necessary pieces of equipment for dry granulation are first a machine for processing the dry powders and second a mill for breaking the compacts so produced.

Sluggers

The dry powders can be compressed using a tablet machine or, if higher pressures are required, a heavy duty rotary press can be used. This process is often known as 'slugging', the tablet made in the process being termed a 'slug'. See Chapter 39 for more details.

Roller compactors

Roller compaction is an alternative method, the powder mix being fed between rollers to form a compressed sheet (Fig. 37.10).

A hammer mill is suitable for breaking the compacts or sheets.

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This is Exhibit G referred to in the Declaration of Dr. Michael M. Lipp, sworn this 12th day of November, 2003

Cindy A Sragg

A Commissioner, Notary Public
for taking oaths

CINDY A. SRAGG
Notary Public
My Commission Expires
January 23, 2009

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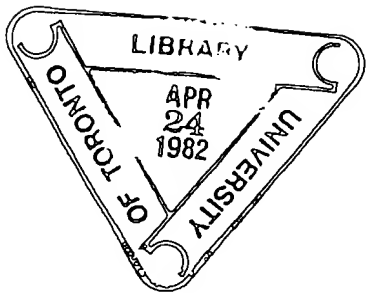

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The authors and publisher have exerted every effort to ensure that drug selection, dosage, and requirements for product labeling (e.g., patient package inserts) set forth in this text are in accord with current recommendations and practice at the time of publication. However, in view of ongoing research, changes in government regulations, and the constant flow of information relating to drug therapy and drug reactions, the reader is urged to check the package insert for each drug for any change in indications and dosage and for added warnings and precautions. This is particularly important when the recommended agent is a new or infrequently employed drug.

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7

Oral Drug-Delivery Systems for Prescription Pharmacy

John L. Colaizzi
William H. Pitlick

Oral drug-delivery systems represent a composite of great clinical importance, wide product variety, and extreme pharmaceutic complexity. The importance of the oral drug-delivery systems arises out of the fact that they are the most highly used dosage forms for medication administration. Whether one tallies their proportion among hospital and long-term care facility medication orders for inpatients, the percentage of oral dosage forms among prescriptions for ambulatory patients, or the kinds of dosage forms encountered among the myriad of over-the-counter (OTC) medications, the clear majority of the dosage forms in which medications are administered are oral forms. The variety of oral medication forms relates to their availability as liquids or solids, for immediate or prolonged release, and for local gastrointestinal or systemic effects. The pharmaceutic complexity of oral forms is due to the many stability, palatability, and bioavailability variables which must be considered in the design and formulation of the many types of liquids and solids that are used for the administration of oral medications.

This chapter stresses those features of the oral drug-delivery systems that are important to pharmacists in their daily work with patients as well as with other health practitioners. A major responsibility of present-day pharmacists is to advise, to counsel, and to perform a consultative service role to all that they serve. Consequently, a primary objective of this chapter is to provide the student

or pharmacist with a basis to advise authoritatively on the proper choice of oral dosage forms (*e.g.*, when they should and should not be used, which specific types should be used in certain clinical situations), how they should be employed for the most effective results, and very importantly, how to select the best quality drug product at a reasonable cost for the patient.

The reason that the issue of the pharmacist's role in the selection of the specific supplier of the dosage form to be dispensed, from among chemically equivalent products, becomes so essential to a discussion of the educational objectives of this chapter is because the vast majority of product selection decisions relate to oral forms of medications. Because oral medications are the most widely used, there has been an interest among the so-called generic manufacturers to make such products available. Table 7–1 indicates the most frequently prescribed products for which a brand is unspecified by the physician, and as can be seen, a wide range of oral products is evident. In addition, questions of assessing bioequivalency in terms of bioavailability and dissolution concepts have been strongly oriented toward oral dosage forms. Even certain difficult problems that relate to chemical equivalency, such as weight variation and content uniformity requirements, have been more relevant to oral dosage forms than to any others. Thus, the pharmacist's increased involvement in drug product selection has made an understanding of oral drug-delivery systems of very practical importance.

Although pharmacists no longer routinely engage in the extemporaneous preparation or compounding of oral dosage forms in general practice, there are occasions when such compounding ability may be of importance. When working with pediatric patients, geriatric patients, or other patients unable to swallow solid dosage forms, the pharmacist may be called upon to formulate and prepare special liquid forms of drugs that are commercially available only in solid dosage forms. Flavor, stability, and uniformity become important considerations in such situations. Another example would be the preparation of a special dose of medication, either much higher or much lower than the doses in commercially available dosage forms. There are other times when a pharmacist must decide how, or if, an oral form of a particular medication or combination of medications can be prepared when

Table 7–1. Most Frequently Prescribed Drugs by Generic Name

RANK	DRUG	USUAL ORAL DRUG FORMS
1	Ampicillin	Capsules, Suspension
2	Tetracycline (systemic)	Capsules, Suspension
3	Penicillin VK	Tablets, Solution
4	Erythromycin salts or esters (systemic)	Tablets, Suspension
5	Prednisone	Tablets
6	Amoxicillin	Capsules, Suspension
7	Phenobarbital	Tablets, Elixir
8	Penicillin G (systemic)	Tablets, Solution
9	Digoxin	Tablets, Elixir
10	Hydrochlorothiazide	Tablets
11	Meprobamate	Tablets, Suspension
12	Thyroid	Tablets
13	Nitroglycerin	Sublingual Tablets
14	Erythromycin base (systemic)	Tablets
15	Paregoric	Tincture
16	APC with Codeine	Capsules, Tablets
17	Potassium Chloride	Enteric-coated Tablets, Elixir
18	Hydrocortisone (dermatologic)	
19	Ferrous Sulfate	Tablets, Elixir, Syrup
20	Quinidine Sulfate	Tablets

(Adapted from National Prescription Audit, IMS America, 17th ed. Ambler, PA, 1978)

not available commercially. A phramacist should be able to apply pharmaceutic principles to the process of extemporaneous compounding to prepare an appropriate dosage form that meets the physician's intent and the patient's needs.

In summary, a very important objective of this chapter is to give a thorough enough understanding of the pharmaceutics of oral medications:

1. To enable the pharmacist to make decisions and to provide advice on the proper choice and use of oral forms for given patients and specific drugs
2. To enable the pharmacist to safely and responsibly engage in the selection of oral drug products
3. To enable the pharmacist to design and prepare extemporaneous formulations of oral medications whenever the need to do so occurs

It should be pointed out that many pharmacists, working primarily in the pharmaceutical industry, engage in research and development activities, production activities, and control functions involving oral medications—both solid and liquid. While many of these pharmacists have advanced education in specialty areas, there are also numerous positions filled by pharmacists at the first professional degree level. The approach of this chapter is a clinical one and stresses aspects of knowledge about oral medications that will be eminently important in community and hospital pharmacy practice. However, the concepts of oral drug-delivery systems presented throughout this chapter should also serve as a foundation upon which more highly technical, industrially oriented information might be superimposed for the more specific needs of those pharmacists who wish to pursue specialized careers in the pharmaceutical industry.

THE ORAL ROUTE OF ADMINISTRATION

ANATOMIC AND PHYSIOLOGIC FEATURES

From the earliest records of drug use, the oral route has been the natural and preferable means to administer drugs. This preference has continued to the present day—so if a prescription or drug order specifies a drug entity and a dose without specifying the route of administration, one may assume, based on its acceptance as the preferred and most convenient method of administration, that the oral route is intended. Even our ancient counterparts recognized that certain preparations could be used throughout the alimentary canal for local as well as systemic effects. Today, dosage forms can be formulated to act on or be absorbed at various, somewhat specific sites, following oral administration. In a sense, the oral route actually comprises several sites for the systemic absorption of medication. One may appreciate this more by studying the anatomy and physiology of the digestive system.

The alimentary canal consists of about 9 meters of mucous membrane—lined musculature commencing at the mouth. Sites for local drug action or drug absorption, include in anatomic order, the mouth and buccal cavity, tongue, pharynx, esophagus, stomach, small and large intestine.

The mouth consists of two parts: (1) the vestibule, which is the space bounded externally by the lips and internally by the teeth and gums, and (2) the mouth cavity proper, delineated by the hard and soft palates above and the tongue below. The remainder of the cavity is formed by mucous membrane that begins under the tongue, continues up the side of the cavity, and includes the gum lining. The buccal cavity or buccal pouch, a site for drug absorption, constitutes the posterior boundary of the vestibule formed by the reflection of the interior mucous membrane of the cheek onto the upper and lower jaw. Blood supply to the buccal pouch and to other parts of the oral cavity originates from the maxillary artery, a branch of the external carotid artery, which in turn arises from the common carotid artery. The venous blood is drained by the buccal vein through the pterygoid plexus into the internal jugular vein.

The tongue is principally a sense organ and assists in mastication and deglutition of food. The inferior aspect of the tongue, however, is connected to the mandible by the mucous membrane reflected over the floor of the mouth to the lingual surface. As such, this area is also a site for drug absorption, specifically for sublingual dosage forms. The sublingual area is drained by the sublinqual vein which also empties into the internal jugular vein. Teeth are composed of enamel, dentin, pulp, and ce-

mentum. The enamel is an extremely hard, thin crust over the dentin. Nevertheless, during the period of its formation, enamel may be penetrated and stained by certain drugs and chemicals, such as fluorides and the tetracyclines. Dentin is osseous tissue which may also stain if there are cracks or fissures in the enamel.

The pharynx is that part of the digestive tube connecting the oral cavity with the esophagus. The pharynx may be a site for local application of drugs and, if residence time is sufficient, as in the case of certain topical applications, it may become a syst mic absorption site. Thus, local anesthetics applied topically within the oral cavity, for example, could potentially exert some systemic side-effects. Pharyngeal veins originating in the pharyngeal plexus open into the internal jugular or, occasionally, into the superior thyroid vein. Thus, drugs absorbed from the vestibule, oral cavity, or pharynx bypass the mesenteric circulation (and first pass through the liver) and then enter the systemic circulation directly.

The great majority of drugs administered by the oral route, however, are intended for systemic action, and are primarily absorbed from the stomach and upper portion of the small intestine. The upper part of the stomach does little more than collect food. The mixing and digesting of food occur primarily in the antrum and the pylorus, the entrance to the small intestine. The wall of the stomach is composed of four layers: (1) mucus, (2) submucus, (3) musculature, and (4) serous. A variety f gastric glands extend into the mucous membrane, creating a thick layer. Parietal cells in the stomach wall secrete hydrochloric acid, resulting in a gastric *p*H of approximately 1.0 to 2.5. Epithelial cells lining the stomach secrete mucus that protects the stomach from its high acid concentration. Activity in the stomach, including digestion and propulsion, is controlled by a variety f factors such as meal content, osmolarity, *p*H, and volume. Drug passage through the stomach wall is also influenced by residence time, blood flow to the stomach, *p*H, and other factors.

Thus the complex nature of the stomach's anatomy, and the physiologic processes involved, allow for multiple interactions between the stomach and drugs at this absorption site. The stomach is supplied with blood by three branches of the hepatic artery. Venous blood drains through mesenteric veins or directly into the portal vein, and then passes to the liver.

The small intestine, extending about 7 meters from the pylorus to its juncture with the large intestine, is composed of three parts: (1) the duodenum, (2) jejunum, and (3) ileum. The duodenum is relatively short (about 25 cm). The common bile duct and pancreatic duct enter the duodenum 7 to 10 cm from the pylorus at the sphincter of Oddi. At the pylorus, the *p*H of the duodenum is approximately 4 and increases to 7 or 8 in the jejunum and ileum. The jejunum is approximately 3 meters long with thick, highly vascularized walls.

Two features of intestinal morphology are of note. First, there are the circular folds that project into the lumen of the intestine. These folds extend transversely around the inside of the intestine and are permanent structures, although their size and number vary in the three parts of the intestine. The second feature of note are the villi, tiny fingerlike projections, barely visible but completely covering the interior surface of the small intestine. The folds and villi begin just past the sphincter of Oddi and lessen in size and frequency toward the terminal end of the ileum. The significance of the folds and villi to drug absorption is that they provide a tremendous increase in membrane surface area through which drug molecules may pass. Blood from the small intestine is drained principally by the inferior and superior mesenteric veins which are tributaries of the portal vein leading to the liver. For all practical purposes systemic drug absorption following oral administration does not extend beyond the terminal portion of the small intestine. However, a number of drugs, particularly laxatives, antacids, and nonabsorbable anti-infectives may be taken orally for local effects in the colon or large intestine. The colon is about 1.5 meters in length. The principal function of the large intestine is to conduct indigestible material to the exterior in the feces, with a large amount of the water content of the intestinal contents being absorbed in the process. The mucous membrane of the colon is smooth and the intestinal wall is made up of longitudinal and circular musculature. This musculature is relatively sensitive and responds readily to stimulus. Over-stimulation, however, such as in chronic use of laxatives, may lead to loss of tone and reduction

in the colon's availability to respond to stimulus. Systemic absorption of rectally administered drugs is discussed in Chapter 12.

Anatomically, then, the oral route of administration represents several possible sites for local drug action and systemic drug absorption. It has been shown that drugs taken by mouth may be either absorbed locally or absorbed from the stomach or intestine. However, there are a number of physicochemical and physiologic factors that must be considered in light of differences in anatomic structure along the alimentary canal.

PHYSICOCHEMICAL FACTORS IN DRUG ABSORPTION BY THE ORAL ROUTE

The absorption of drugs at a particular site in the gastrointestinal tract is a function of several closely related variables including the degree of ionization, lipid solubility, electrical charge, molecular size, and presence of active transport systems.

In general, because of their lipid solubility, only un-ionized drug molecules are absorbed. Because most drugs are weak acids or bases and the *p*H along the alimentary canal ranges from 1 to 8, a wide spectrum of ionization degree exists for most drugs as they progress along the gastrointestinal tract. In different regions, a given drug may be completely ionized or completely un-ionized. For example, a weak base such as quinidine is essentially completely ionized in the acid environment of the stomach and is poorly absorbed there. On the other hand, in the less acidic, slightly alkaline, small intestine it is almost completely un-ionized and absorbed quite well.

Closely related to ionization is the lipid/water partitioning of a drug. Because membranes are predominantly lipids while intraluminal fluids are aqueous, drugs must be able to pass from the aqueous to lipid phase in the process of absorption. Ionized species are poorly lipid soluble and consequently do not easily pass through membranes. Special mechanisms are found in membranes for the absorption of small molecule electrolyte drugs. Water-filled pores may have electrical charges that influence movement of anions or cations. Some hydrophilic species may also pass through membranes by way of these water-filled pores. Finally, there may be enzyme-mediated transport processes or active transport processes for "pumping" drug molecules across a membrane. More detail on these concepts of biopharmaceutics is found in Chapter 4.

PHYSIOLOGIC FACTORS IN DRUG ABSORPTION BY THE ORAL ROUTE

In general, the higher up the alimentary canal a drug is absorbed, the more rapidly it will act. Concentrations of drug at the absorption site are usually highest in the mouth, and drugs absorbed from the oral cavity enter the systemic circulation directly. Thus buccal and sublingual dosage forms are usually associated with a very rapid onset of action.

As the drug moves down the alimentary canal, it becomes progressively diluted by secretions and by mixing with foods and liquids, and its concentration at the absorption site is reduced. In addition, other factors described in this section influence drug absorption in the gastrointestinal tract.

Hydrogen Ion Concentration

As noted, *p*H differences throughout the gastrointestinal tract are very influential in determining drug absorption because they affect ionization and lipid partitioning. The *p*H may also affect the stability and bioavailability of drugs, because some drugs are either very unstable or poorly soluble in an acid or base environment.

Motility

Gastrointestinal motility may enhance or reduce a given drug's absorption by moving it either toward or away from its optimal absorption site. For example, if a drug is predominantly absorbed in the stomach, stimulation of gastric emptying will hasten drug removal from the absorption site and reduce absorption.

Blood Flow

Increased blood flow to the intestines results in absorbed drug being carried more rapidly from the absorption site. Several studies have shown that certain types of food affect blood flow to the gastrointestinal tract. For example, blood flow to the intestines is increased by a protein meal but not affected by a carbohydrate meal. Enhanced adrenergic states, such as fear or anxiety, may also reduce gastrointestinal blood flow.

Secretions

As previously noted, gastrointestinal secretions modify *p*H, leading to changes in the lipid-water partitioning of drugs. Such secretions can also reduce drug concentrations by simple dilution and by hydrolyzing esters and peptides that may also destroy drugs (*e.g.*, insulin or oxytocin) and thus render them ineffective by the oral route. Excessive secretions of mucus, as seen in certain forms of gastroenteritis, may reduce absorption by coating the intestinal mucosa. Bile salts solubilize fats to enhance their absorption. They also have surface-active (wetting) properties, and may thus benefit the absorption of some drugs.

Food

The presence of food in the gastrointestinal tract may affect drug absorption. Food delays the emptying of drugs from the stomach and may also alter *p*H, change the solubility of the drug, dilute or physically limit drug access to gastrointestinal mucous membranes, decrease gastric emptying rate, or increase intestinal blood flow. Depending on the site of drug absorption one or several of the above factors may alter the rate and extent of drug absorption.

SPECIAL VARIATIONS OF THE ORAL ROUTE

Because it can readily be seen that there are several distinct sites for absorption from the alimentary canal, methods of drug administration and special oral drug-delivery systems have been designed to concentrate drugs directly at these sites.

Buccal and Sublingual

Drugs may be administered and absorbed from two sites in the oral cavity. Special dosage forms have been designed for drugs intended for manual placement either in the buccal pouch between the cheek and gums, or under the tongue. These doage forms are buccal and sublingual tablets, respectively. Buccal tablets may be designed for either rapid disintegration and dissolution or for slow erosion and prolonged absorption. Hormones such as progesterone and oxytocin, which may be destroyed by gastric acid, can be given as buccal tablets.

Sublingual tablets are comparatively small and generally all completely soluble. They are designed for very rapid disintegration and dissolution when placed under the tongue. Examples of popularly used sublingual tablets are the organic nitrates and nitroglycerin. Because these coronary vasodilators are intended for rapid onset of action, the sublingual route proves particularly useful. Patients who are taking sublingual or buccal tablets must be advised not to take them with water or other fluids and to refrain from eating, chewing, or smoking during the administration period, so that the tablet will not become dislodged and swallowed. The administered tablets must remain undisturbed until completely dissolved. Buccal and sublingual tablets should be formulated to be as bland and tasteless as possible to reduce salivation and swallowing.

The possibility of rapid absorption is a significant advantage of the buccal and sublingual routes of administartion. These routes may also be preferred for patients who cannot swallow, although the parenteral route (or less often, the rectal systemic route) is a more common alternative. In addition, it is possible to administer drugs, which might be destroyed by the gastric or intestinal juices, orally. Finally, the buccal and sublingual routes share the advantages of parenteral routes of administration—in addition to the fast onset of action, the drug is not subject to immediate metabolism, that is first-pass metabolism by the liver. Following absorption from the oral cavity, drugs enter the systemic circulation directly and bypass the hepatoportal circulation.

Pharyngeal

When local effects in the oral cavity or pharynx are desired, drugs may be delivered to the site of action by lozenges or troches (formerly also called pastilles). Lozenges are usually discs or squares composed of medication, sugar, flavors, and adhesive agents such as acacia, methylcellulose, carboxymethylcellulose, or similar materials. Cough drops are examples of lozenges. Troches are a type of lozenge made of medication, sugar, flavors, and a gum which is molded or dried. Troches and lozenges are designed to dissolve slowly. Even with this in mind, however, they do not generally provide enough contact time to exert any meaningful antimicrobial effects. Therefore, they should not contain antibiotics, and even the use of other antimicrobial agents (antiseptics) with these dosage forms is of limited or questionable value. Like

mouthwashes and gargles, these dosage forms stimulate the production f oral secretions and thus can provide a comforting and demulcent effect in minor throat or oral cavity irritations.

Nasogastric

The nasogastric route is a form of oral administration which is sometimes used in hospitalized patients who are not able to take oral medications because of an inability to swallow. Such a situation may arise when patients are unconscious, semiconscious, or are unable to swallow because of head or neck surgery, or because of certain neurologic problems. Frequently, a patient will receive all oral nutrition through the nasogastric tube, and this tube can then also be used as a means of administering medications. In these instances, a flexible polyurethane or Teflon plastic tube is passed through the nasopharynx directly into the stomach (or duodenum depending on the length of the tube and method of insertion). Of course, in order for medications to be passed through a nasogastric tube, the medication must be in the liquid state and must be as nonviscous as possible. If tablet or capsule dosage forms must be administered through such a tube, the tablets must first be crushed or the capsules emptied, and the resultant powder must be appropriately suspended or dissolved in an aqueous liquid.

LIMITATIONS OF THE ORAL ROUTE

The oral route of administration is the most common and popular method for the administration of medication because it is simple, convenient, and usually painless. The oral route is always the preferred route of administration unless another route offers specific advantages. Nonetheless, the oral route does have certain limitations and they must be kept in mind when choosing a method of drug delivery.

The major limitations of the oral route relate to the absorption process variables that determine the rate and extent of drug entry to the circulation. The variables associated with the gastrointestinal absorption process make the oral route of drug administration more irregular and less predictable therapeutically than parenteral routes. It is not always possible, because of limitations imposed by the absorption process, to achieve high enough blood levels using oral medications. In cases of serious systemic infections, like spinal meningitis, much higher serum levels of drug may be required in order to penetrate certain body tissues, and it would be impractical to try to achieve such levels using oral administration. The doses that would have to be administered would be too large because oral drug administration rarely leads to 100% absorption. In such cases parenteral administration is preferable. Similarly, certain drugs must always be administered parenterally because of poor or unreliable absorption from the gastrointestinal tract. This may be due to poor intrinsic absorption from the gastrointestinal mucosa (*e.g.*, gentamicin) or to a high degree of instability in the gastrointestinal tract (*e.g.*, insulin). Sometimes drugs that can be administered orally under normal circumstances must be administered parenterally when a very rapid or immediate therapeutic response is required, for example, when a patient is in a hypotensive or hypertensive crisis. In such cases the oral route would not be suitable because of the time required for the absorption process to bring about a serum level of drug sufficiently high to cause a therapeutic response. While it is possible to achieve therapeutic blood levels sooner by increasing the initial or loading dose of the oral medication, it is not generally possible to achieve therapeutic effects as immediately as can be obtained by parenteral routes.

Oral medications present a difficulty in patients who either cannot, or will not, swallow. Patients who have had surgery involving the throat, esophagus, or other areas of the upper gastrointestinal tract may not be able to swallow. Patients who are unconscious are similarly unable to swallow. Unless such patients have a nasogastric tube, it is not possible to give them oral medications. Certain patients, particularly psychiatric patients, may occasionally be in a hyperdisturbed state, causing them to refuse oral medication. In such situations it is generally necessary to resort to injections. The oral route may also be unreliable in patients who are suffering from nausea or vomiting. Even if such patients are able to swallow such medications, the drug itself might be lost from the gastrointestinal tract before absorption is complete if vomiting occurs. For patients in this category, the rectal route is often a suitable alternative.

PALATABILITY—A SPECIAL REQUIREMENT FOR ORAL MEDICATIONS

IMPORTANCE OF PALATABILITY TO THERAPEUTIC SUCCESS

In various historical settings it has sometimes been believed that a medication would be more effective if it was difficult, painful, or at least unpleasant to take. Thus, for example, it was once thought that the more foul tasting an oral liquid might be, the greater the therapeutic effect. However, it is now clearly recognized that patients, already uncomfortable from the effects of the pathologic condition for which they are being treated, will benefit most from medication if its administration is not unpleasant. Palatability is also directly linked to the problem of patient compliance, because if patients experience apprehension and stress when the medication is administered, it is likely that they will tend to avoid their medication. This is especially true for medications that need to be taken chronically, or for oral liquids in large doses. Dosage forms for pediatric patients require particular attention to favorable palatability characteristics. Many children simply will not take oral medications that are unpleasant and exhibit poor palatability. Equivalent oral dosage forms—particularly pediatric solutions, syrups, and suspensions—that may be equivalent in bioavailability and chemical potency often cannot be substituted because of a difference in palatability resulting in the refusal of some children to take the substituted medication.

Palatability, which in its broadest sense means acceptability, is most commonly associated with oral liquids and chewable tablets. But it also applies to other oral dosage forms as well. For example, the use of hard-shell gelatin capsules is really intended to facilitate the administration of powdered substances that might otherwise be difficult to administer and that might be unpleasant tasting. Coatings on tablets can serve many different purposes, but sometimes they are intended to make the tablet easier to swallow, especially if the tablet contains a bitter-tasting drug. Tablets or capsules that are excessively large will also have their over-all dosage form palatability reduced. Virtually any feature of a dosage form that is designed to improve patient compliance can contribute to palatability. The reader is also referred to a discussion of patient acceptance considerations in Chapter 5.

FACTORS AFFECTING PALATABILITY

Palatability of an oral dosage form may be strongly influenced by psychological, chemical, and physical reactions and perceptions on the part of the patient about the medication. With the possible exception of hearing, the five senses are involved in a patient's perception of palatability. Sight is important because the total appearance of the drug product and the individual dosage units are important. A smooth and shiny coated tablet may be more acceptable to some patients than an uncoated plain tablet. Even though charcoal does not exhibit any taste, its black color contributes markedly to its inherent unacceptability to children when slurries or other forms of charcoal are administered as adsorbent therapy in treating accidental poisonings. That appearance is an important component of acceptability and palatability is certainly demonstrated by the importance of color in pharmaceutical dosage forms. Color can be an important factor in palatability. Oral liquid dosage forms have traditionally been colored to match their flavor. This has recently become more difficult to accomplish in commercial prescription products because due to their carcinogenic characteristics in laboratory animals, some commonly used FD&C dyes have been withdrawn from use.

A good illustration of the relationship between color, acceptability, and therapeutic efficacy of dosage forms has been shown in a statistically designed study in which 96 hospitalized patients were asked to compare the effects of the orange and blue capsules of a hypnotic and a placebo. Women could not differentiate between active drug and placebo when the capsules were blue, but the difference was striking when orange capsules were used. Although men were less affected than women by color, men did show better discrimination of drug from placebo with blue capsules than with orange. Capsule color clearly had an effect on the hypnotic action of the medication. This study illustrates that visual factors such as color can contribute to a medication's ultimate therapeutic outcome.

The sensation of touch is a component of dosage form palatability, demonstrated by the importance of texture, "mouth feel," grittiness, chalkiness, viscosity, and a sensation of coolness to palatability. Chewable tablets are more palatable

if they are not gritty or chalky. The use of mannitol as an excipient in such tablets serves not only to sweeten, but also to provide a cooling sensation in the mouth due to its negative heat of solution. In the formulation of oral liquids, viscosity-producing agents such as 0.5 to 1.0% carboxymethylcellulose might be included to produce a texture or mouth feel that is more pleasing. This is particularly helpful when the sucrose content of a syrup is either wholly or partially replaced by synthetic or natural sweetners. Consumers expect syrups, such as cough syrups, to be at least moderately viscous.

Taste and smell are the most important contributors to palatability because they are the key components of the overall sensation of flavor. The taste buds located on the tongue are able to detect four distinct and fundamental taste sensations: (1) sweet, (2) sour, (3) bitter, and (4) salty. In order for a taste sensation to occur, the chemical agent producing the taste needs to be in the form of an aqueous solution, at least to some extent. Therefore, liquid dosage forms of medication containing dissolved drug usually present the most difficult problems when confronted with unpleasant-tasting drugs. It is possible to eliminate or greatly reduce the unpleasant taste sensations associated with some drugs by forming insoluble derivatives. For example, the palmitate ester of chloramphenicol results in a drug form that is so insoluble that it is tasteless, and may be formulated into a pleasant tasting oral suspension, while the parent drug presents a very difficult taste problem. In fact, the suspension dosage form is one of the most effective means to overcome foul-taste problems in liquid dosage forms. This technique is used most frequently for drug administration to pediatric and geriatric patients—the patients most sensitive to unpleasant-tasting medications.

Both pleasant and unpleasant tastes or flavors may be primarily associated with one of the four fundamental taste sensations. However, there are an infinite number of combinations, variations, and gradations possible, and so perceptions of drug taste, in addition to being called salty or bitter, might also be described by terms like metallic or oily. In trying to mask or overcome a foul-tasting drug, flavoring agents that present harmonious combinations, or blend with the taste being masked, can be very helpful. Citrus flavors, for example, have a tart or pleasantly sour taste and are very effective in producing a palatable dosage form. Another approach that may be taken stems from the fact that the tongue's taste buds may be readily desensitized by local anesthetics or aromatic substances. The volatile oils serve as good components of flavor blends for this reason and are useful in masking the taste of unpleasant drugs. Temperature also has an effect on the taste sensations. Very hot or very cold temperatures tend to reduce the intensity of the taste perception. A slightly cool sensation may improve flavor and palatability.

Smell is very definitely a factor in the overall perception of taste and flavor. When the olfaction capabilities are dulled because of a head cold or sinus congestion, the patient is less able to detect flavors or to preceive tastes. In fact, sometimes children will tolerate an unpleasant medication better if they are told to hold their nose so as to avoid smelling the offending substance.

In considering factors that affect palatability of medications, it is also necessary to recall that the perceptions of taste, flavor, and general palatability are subject to the phenomenon of individual preferences. Formulations regarded as palatable to one may be deemed unacceptable to another. But for all of the variables involved, and while admitting that the science of flavoring pharmaceuticals remains one of the most empirical aspects of the formulation process, the vast majority of drugs today are generally available in appealing and palatable forms far surpassing some of the ghastly preparations that pharmacists compounded for patients 30 or more years ago. Today, patients usually expect their medications to be palatable, and pharmacists have a responsibility to meet this expectation.

FLAVORING ORAL DOSAGE FORMS

It is not uncommon for the pharmacist to employ flavoring techniques in the daily practice of pharmacy. In pediatric work, for example, it may be necessary to prepare a liquid form of a drug that is commercially available only in tablet or capsule form. Similarly, it may be necessary to prepare a more diluted form of an oral drug in order to give a very low dose (*e.g.*, for an infant). In such situations an acceptable flavor can often be achieved by dissolving or suspending the drug (or the drug

and excipients if a crushed or triturated tablet or the contents of a hard-shell gelatin capsule are employed) in a flavored vehicle. A number of suitable flavoring vehicles useful for this purpose are listed in Table 7-2. In the dispensing and labeling of such extemporaneous liquid products it is a good practice to recommend that the product be refrigerated. Because such products may not be adequately preserved (unless they contain 20% or more alcohol) they may be prone to bacterial and mold growth, especially at room temperature and above. Refrigeration will better assure that such growth does not become a problem. The pharmacist should also identify a date for discarding any unused medication on the label (*i.e.*, after a time corresponding to the prescribed period of use for the quantity dispensed). This should be done for two reasons: (1) the fact that the product may not be adequately preserved as previously cited, and (2) the uncertainty that may exist over the longer-term chemical stability of such extemporaneous products.

The use of flavor vehicles such as those listed in Table 7-2 provides a simple and effective approach to flavoring extemporaneously prepared liquids that are intended for short-term use. If formulations are intended for long-term use, then stability studies on all components of the preparation are necessary to ensure an adequate shelf life for the product. This is also true of the flavor components, which tend to be relatively unstable.

In designing a flavor blend, which is the approach that is used when commercial products are being designed, "flavor guides" provided by companies that specialize in flavoring agents are available. Fritzshe Brothers, Inc, of New York City, is one such company. In addition to providing publications that summarize their many flavoring agents, the flavor houses are quite willing to provide information to pharmacists who need to prepare special flavoring blends for special formulations or investigational drugs. The many synthetic flavors that these companies have available cover a wide range of flavoring agents. Frequently, two or more of these are blended to provide optimal masking characteristics for a given drug substance. While the majority of these synthetic flavors are available in liquid forms, many are also available as spray dried powders which are suitable for flavoring chewable tablets. These spray dried powders offer greater stability in chewable tablets than is possible by simply incorporating volatile oils as flavoring agents.

Sweetening Agents

The addition of a sweetening agent is an important factor in designing flavor into pharmaceutical dosage forms. Sucrose has traditionally been the standard sweetener in syrups and other oral liquid dosage forms, and it provides good sweetness properties and reasonably good stability properties. Other sugars like glucose and fructose may also be

Table 7–2. Common Flavor Vehicles for Extemporaneous Compounding of Liquid Oral Dosage Forms

Acacia syrup NF	A vanilla-flavored vehicle suitable for masking salty drugs.
Aromatic elixir NF	Preserved with sodium benzoate
Cherry syrup NF	A pleasant flavoring agent if 20% alcohol is desirable
	This syrup contains no preservative and has a slightly acid *p*H.
Coca-Cola syrup	A very popular flavoring vehicle
Cocoa syrup NF	If not easily available commercially, this syrup can be easily prepared by the pharmacist. Good for masking bitter-tasting drugs
Peppermint water NF	A suitable vehicle if sweetness is not desired
Raspberry syrup USP XVIII	Except for the taste, it has properties similar to cherry syrup.
Tolu Balsam syrup NF	Pleasant aromatic taste
Wild Cherry syrup USP XVIII	Not a fruit syrup, but useful in masking the taste of bitter substances

used alone or in combinations to provide different degrees of sweetness or improved stability properties. Polyols such as glycerin, sorbitol, mannitol, and propylene glycol are chemically related to the carbohydrates but are not sugars. They provide some sweetening properties but much less so than sucrose, glucose (which is also somewhat less sweet than sucrose), or fructose (which is somewhat sweeter than sucrose). When sucrose poses stability problems, as with certain acids, glucose may be useful as an alternative sweetener, or it may be necessary to use one of the polyols. Glycerin, sorbitol, mannitol, and propylene glycol also provide fewer calories than the sugars. Although each is ultimately metabolized to glucose in the body, they do not elevate blood glucose levels as much or as fast as carbohydrate administration. Therefore they are useful in liquid preparations that do not have to be totally nonnutritive, but where lower caloric content and reduced glucogenic properties are desirable. They also have solvent properties and may be useful as cosolvents. These polyols add a favorable viscosity to pharmaceutical liquids and also aid in retarding cap-locking (which occurs because sugars crystallize in the cap threads). Because of these favorable formulation characteristics, sorbitol and other polyhydric alcohols have become widely used ingredients in oral liquids, and 70% sorbitol solution is purchased in large quantities by pharmaceutical manufacturers because it is an ingredient of many commercially available liquid pharmaceuticals. The excellent texture imported by sorbitol, together with its stability-enhancing qualities has caused its popularity to increase in recent years.

With the controversial Food and Drug Administration (FDA) removal of the synthetic, nonnutritive sweeteners, sodium and calcium cyclamate, from the list of substances classified as "Generally Recognized as Safe," only saccharin remains available as a suitable noncaloric and nonglucogenic sweetener. Saccharin in a concentration of 0.1% provides an adequate degree of sweetness in many pharmaceutical liquids, although this concentration may be varied somewhat to obtain a degree of sweetness adjusted to the needs of the specific formulation. One problem that is associated with the use of saccharin as an artificial sweetener is its ability to cause a bitter aftertaste. This was less of a problem with the cyclamate sweeteners, and attempts to develop improved nonnutritive sweeteners that avoid the after-taste problems and that are acceptable to FDA from a safety point of view are underway. As noted previously, the low concentrations needed for nonnutritive sweeteners like saccharin, do not impart the viscosity, texture, or desirable mouth-feel characteristics of simple syrup (85% sucrose) or a 70% sorbitol solution. As a result, texture or viscosity adjusters such as 1 to 2% sodium carboxymethylcellulose or sodium alginate may be employed.

Flavor Evaluation

Evaluation of flavoring still tends to be a somewhat empirical procedure, but the use of taste-testing panels to evaluate candidate flavor formulations can be very helpful. Panels commonly used range from a half-dozen to over fifty subjects, and the panel's reactions to a series of test flavor formulations for a particular drug product can be analyzed statistically to provide valuable information on selecting the flavor that is most likely to please the greatest number of patients who are ultimately going to receive the medication. In carrying out the tests, it is important to recognize that taste fatigue is a factor that affects most individuals quickly, and it is necessary to allow adequate time between evaluations in order to obtain meaningful results. From another point of view, it must be recognized that certain flavors become monotonous if they have to be taken daily, and sometimes several times a day, for extended periods of time. Antacids are an example of such a product, and it is thought that less exotic flavors, such as peppermint, might be best for these kinds of products. In evaluating flavors by the test-panel technique it is essential to recognize that flavor preference is highly age related. Therefore, if a formulation is intended for pediatric use, an appropriate test panel of children should be employed. Increasingly stringent regulations on the use of human subjects in drug testing—even taste testing—is making such evaluation increasingly difficult.

COLOR AS A CONTRIBUTOR TO PALATABILITY IN ORAL DOSAGE FORMS

Color plays a role in determining the acceptability and elegance of nearly all dosage forms and is especially important as a component in the palat-

ability of oral dosage forms. In oral liquids or chewable tablets, the color can enhance the flavor if the two are carefully coordinated. Accordingly, one would normally expect a grape-flavored cough medicine to be purple, and a cherry-flavored antibiotic pediatric suspension to be red. Occasionally, however, a noncorresponding color may be used as a psychological distraction to draw attention away from a particularly difficult-to-mask bitter or otherwise poor-tasting drug. Besides using color as a means of flavor enhancement, it also provides a valuable means to establish product identity and to improve the aesthetic qualities of a dosage form.

Color in oral medications is by no means limited to liquids, for tablets, and especially coated tablets, are usually colored. The same is true for capsules. The inclusion of colors poses certain formulation problems that no doubt affect the industrial pharmacist more directly than the community and hospital pharmacy practitioner. One of these problems relates to difficulties in duplicating the same color from batch to batch. Because colorants are used in exceedingly small concentrations, any slight variation can result in an altered shade or hue of color that will be noticeable when one lot of the product is compared with another. Another problem is color stability. Dyes and other colorants frequently fade, especially if they are exposed to ultraviolet light over a period of time. Color changes may also be induced if the coloring agent interacts with the drug or other excipients in the formulation. In addition, dyes may occasionally alter the physicochemical or biopharmaceutic properties of the dosage form. For example, the disintegration of gelatin in capsules may be altered by certain dyes.

Natural colorants like caramel, cudbear, and chlorophyll are sometimes used, but the majority of coloring agents in modern pharmaceutical products are synthetic dyes, referred to as coal tar dyes, a name that reflects the original source of reactants from which many of these compounds were synthesized. These colorants may only be used for human consumption if they are regarded as safe by the FDA under the provision of the Color Additive Amendment of the Federal Food, Drug and Cosmetic (FDC) Act which was put into effect in 1960. These FDA-approved colorants are usually classified as FD & C, D & C, or Ext D & C, to designate that they may be used in foods, drugs, and cosmetics; drugs and cosmetics; or external drugs and cosmetics, respectively. Of course, only the first two categories are applicable to oral dosage forms. A numerical designation is used for each color dye in each certified category, and sometimes a common name may be used as well. FD & C Yellow No. 5, for example, is alternatively called tartrazine, and FD & C Blue No. 1 is called Brilliant Blue. Some of these colorants are water soluble, others are alcohol soluble, and still others are primarily intended to dissolve in oils. Some of the water-insoluble types may be referred to as pigments, a term that also applies to certain insoluble plant constituents or minerals like titanium dioxide, red ferric oxide, or yellow ferric oxide. Pigments are used to render gelatin capsules opaque. Some water-soluble dyes may be rendered insoluble by adsorption onto solid substrates such as alumina. The resultant adsorbate complex is referred to as a color lake. Occasionally, the safety of a certified material may come into question in light of new findings from a toxicity study, and FDA may withdraw the substance from the approved and certified list. Such actions will force the manufacturers to reformulate products that may have contained the colorant that was decertified. It may be impossible to reproduce the original color exactly, in which case the pharmacist may be called upon to explain a product's color change to patients who continue to use the product. While colorants are desirable in most oral dosage forms, their appearance, safety, and efficacy can generally be optimized if the lowest possible quantities of dyes and other coloring agents are used.

SELECTING BETWEEN A LIQUID AND A SOLID ORAL DOSAGE FORM

LIQUID OR SOLID FORMS

The choice of a specific dosage form as an appropriate drug-delivery system usually depends on the physicochemical nature of the drug and on the therapeutic intent. Therapeutic intent depends on the disease or physiologic state that is being treated and on individual patient characteristics. Consideration of these factors usually determines whether an oral medication should be administered as a liquid or as a solid dosage form. Physicochemical determinants of dosage form for oral drugs are

primarily related to bulkiness, stability, taste, and bioavailability. Factors that primarily pertain to the patient include ease of administration, dosage flexibility, and dosage accuracy.

PHYSICOCHEMICAL-RELATED DETERMINANTS

The *bulkiness* of a drug might become a factor in choosing between a liquid and a solid oral dosage form when the amount of drug required for a dose and the bulk density of the powdered form of the drug are such that the bulk of drug that is needed is very large. The problem would be evidenced in that any tablet or capsule that might be formulated would be too large for convenient administration. Drug doses larger than 0.5 to 0.7 g are difficult to accommodate in a single tablet or capsule. Very large tables or capsules are not only unattractive, but are difficult to swallow as well. The need to administer multiple tablets or capsules for a single dose is less than desirable. Therefore, such a drug can often be better accommodated in a liquid dosage form. If the drug entity is soluble, a syrup or an elixir may be formulated, and if it is not suitable for a solution dosage form, then an oral suspension may be used. Drug doses as large as 5 g are accommodated in a single dose of some liquid products (suspensions).

Stability, especially chemical stability, can have an important influence on whether a drug is ultimately formulated into a solid oral dosage form, a liquid form, or both. In general, solid dosage forms like tablets and capsules exhibit fewer stability problems because they exclude water. While drugs can undergo chemical decomposition in solid dosage forms, the potential for hydrolysis and oxidative decomposition is enhanced in the presence of aqueous solvent systems or dispersion media that have water as a base. Aspirin is a classic example of a drug that has traditionally been unavailable in a suitable liquid dosage form because of its inherent instability in the presence of aqueous systems because of hydrolytic degradation. Part of the reason for the great increase in the popularity of acetaminophen as an alternative to aspirin is because it is available in both solid and liquid oral dosage forms. The penicillins are also unstable in aqueous systems, and liquid dosage forms of these drugs must be reconstituted into solutions or suspensions at the time of dispensing, after which their potency is retained at a suitable level for a relatively limited period of time. Reconstituted oral liquid forms of penicillin, if refrigerated, can only be used for a period of not more than two weeks after reconstitution. Occasionally a relatively insoluble derivative of a drug may be developed, permitting the formulation of a liquid dosage form that would otherwise have been impossible because of stability limitations. The water-insoluble salt, propoxyphene napsylate, is an example of a derivative for which an aqueous suspension dosage form is available, even though one was not available for the earlier hydrochloride salt form of the drug.

The *taste* of drugs also has a bearing on whether or not oral dosage forms must be limited to solid dosage forms or whether liquid forms are possible. Capsules and coated tablets can completely eliminate taste problems with drugs, and uncoated tablets can usually be swallowed quickly enough to avoid any bitter or otherwise unpleasant taste. If drugs are foul tasting, they may not be able to be formulated into oral liquid forms unless insoluble derivatives can be prepared and placed in suspension. Some drugs, (quinine, Atabrine, and some antibiotics) are among the most bitter substances known to man.

Bioavailability problems are usually related to a slow or inadequate disintegration or dissolution of the drug from the dosage form in which it was administered. In general, liquid dosage forms present fewer bioavailability problems than solid dosage forms, and solutions such as syrups and elixirs are more immune to bioavailability problems than are suspensions. Occasionally, a solid dosage form might cause a bioavailability or dissolution problem which could be avoided by using a liquid dosage form. Enteric-coated tablets of potassium chloride were once used to provide systemic potassium supplementation, but they led to problems such as intestinal stenosis which resulted from slow and inadequate dissolution and disintegration with particles of the strong electrolyte being localized in contact with gastrointestinal tissue for extended periods of time. This problem is avoided by administering potassium in solution form. Sometimes these differences in bioavailability may be especially pronunced in geriatric patients in whom absorption may be more sluggish. In some cases dose adjustments may have to be made when switching

between solid and liquid dosage forms. The cardiac glycoside digoxin is a good example. The commercially available elixir form provides superior bioavailability to the tablets, and it may be necessary to adjust dose upward or downward when switching a patient between liquid and solid dosage forms. Oral drug products for which *in vivo* bioavailability evidence is likely to be required by the FDA as a condition of marketing are summarized in Table 7-3. These drug products contain active ingredients that the FDA has identified as having actual or potential bioequivalence problems. In addition to those listed in Table 7-3, evidence of bioavailability is also required by FDA for enteric-coated tablets and controlled-release dosage forms. Most controlled-release dosage forms are not available as liquids. It cannot automatically be assumed that a solution of a drug will invariably produce better bioavailability than a tablet or capsule. The drug may precipitate from solution, on striking the aqueous acid stomach contents, or undergo greater decomposition than if administered in solid form.

PATIENT-RELATED DETERMINANTS

Ease of administration of oral dosage forms is often the basis of selection between solid or liquid forms. Many patients find it difficult to swallow solid dosage forms. Infants and young children are rarely able to swallow intact tablets or capsules before the age of about six, and even ten-year-old children are frequently unwilling to try to swallow solid

Table 7–3. Oral Products for which the FDA Requires *In Vivo* Bioavailability Data

CAPSULES	SUSPENSIONS	TABLETS	TABLETS
Calcium Aminosalicylate	Nitrofurantoin	Acetazolamide	Ethinyl estradiol
Potassium Aminosalicylate	Phensuximide	Acetyldigitoxin	Ethoxzolamide
Bishydroxycoumarin	Phenytoin	Alseroxylon	Fludrocortisone acetate
Chlordiazepoxide HCl	Primidone	Aminophylline	Flufenazine hydrochloride
Ethosuximide	Sulfadiazine sodium	Aminosalicylic acid	Fluprednisolone
Methsuximide	Sulfadimethoxine	Aminosalicylic acid and isoniazid	Hydralazine and Reserpine
Paramethadione	Sulfamethoxypyridazine acetyl	Calcium Aminosalicylate	Hydralazine HCl and Hydrochlorothiazide
Phensuximide	Sulfaphenazole	Potassium Aminosalicylate	Hydrochlorothiazide
Procainamide HCl	Sulfisoxazole, acetyl	Sodium Aminosalicylate	Hydrochlorothiazide and Deserpidine
Trimethadione	Triple sulfa	Bendroflumethiazide	Hydrocortisone
Uracil Mustard		Benzoylpas calcium	Hydrocortisone acetate
		Benzthiazide	Hydroflumethiazide
		Betamethasone	Hydroflumethiazide and Reserpine
		Bishydroxycoumarin	Imipramine HCl
		Chlorambucil	Isoproterenol sublingual
		Chlorothiazide	Liothyronine sodium
		Chlorothiazide and Reserpine	Menadione
		Chlorpromazine	Mephenytoin
		Cortisone acetate	Methazolamide
		Deserpidine	Methotrexate
		Dexamethasone	Methylclothiazide
		Dichlorphenamide	Methylclothiazide and Deserpidine
		Dienestrol	Methylprednisolone
		Diethylstilbestrol	Methyltestosterone
		Diethylstilbestrol diphosphate	Nitrofurantoin
		Dyphylline	Oxtriphylline

dosage forms. Although liquid medications are easier to swallow, and are certainly preferred in children, they are inconvenient from several standpoints.

Liquids are bulky, making them more difficult to carry, subject to spilling and imprecise dosing, and they are more difficult to administer while away from home. Tablets and capsules are certainly superior to liquids in this regard. Even in cases in which it has been shown that liquids are more effective than solids (*e.g.*, the oral nonsystemic antacids such as aluminum hydroxide), convenience may dictate that tablets or other nonliquid forms be used while away from home. Chewable tablets offer an excellent alternative in situations of this type because they combine the convenience of administration and the easy portability of solid forms, and yet circumvent the problems associated with swallowing nonchewable tablets or capsules. Oral drops merit special mention as well because they offer an ease of administration not commonly associated with liquid medications. Because they are more concentrated, smaller volumes are needed. They are therefore easier to carry. More importantly, no teaspoon or separate measuring cup is required, and it is less likely that medication will be spilled.

Dosage flexibility is more limited with tablets and capsules than with liquids because the volume of liquid can be varied to give any quantity of dose desired. Using medication measuring cups, dosage may be varied by increments of milliliters or even by smaller increments if calibrated droppers are used. Of course, the particular measuring device employed will determine to what degree the volume may be controlled. With capsules, there is no practical way to vary the dose of the capsule available. If it becomes necessary to provide a dose different from the strengths of capsules available, it would be necessary to empty the contents of one or more capsules and reformulate the contents into a liquid or into extemporaneously prepared capsules of the strength desired. Tablets offer a somewhat greater degree of dosage flexibility than do capsules, in that, if they are scored they may be broken in half or, less frequently, in quarters (see Fig. 7-1).

Dosage accuracy is a definite advantage associated with the use of tablets and capsules. Liquids, on the other hand, can result in dosage inaccuracy depending upon the mode of administration. Although various modern calibrated administration devices, such as plastic dose cups and spoons, are now favored and are frequently dispensed by the pharmacist along with liquid oral prescription medications, the common household teaspoon is still employed in administering oral liquids, and physicians still commonly prescribe such medications in terms of teaspoon dosage units. The term teaspoonful, when used as an indication of a dosing amount, is taken to mean 5 ml. However, the household teaspoons in general use are known to vary considerably, above and below 5 ml, in the volume of liquid that they actually hold. Additional variations occur because such devices are difficult to fill to capacity and are subject to spill. For these reasons pharmacists should discourage the use of household teaspoons as a means to measure and administer medications.

When oral suspensions are used, dosage inaccuracy may result if the suspension has not been sufficiently shaken to uniformly distribute the suspended phase throughout the dispersion medium. Achieving suspension homogeneiety can be difficult at times and depends on how successful the formulator of the suspension has been in achieving easy dispersibility of the suspension. Even if resuspendability is good, the question may remain of how well various patients shake their products to achieve adequate product uniformity.

While the practice of "halving" or, less often, "quartering" tablets offers a measure of dosage flexibility, it is a source of dosage inaccuracy because it is difficult to ensure that the resulting halves or quarters are equal in weight. Sometimes attempts are even made to break unscored tablets using a spatula or razor blade. Such practices should be discouraged, and especially for drugs in which the therapeutic response is sensitive to small dosage variations (*e.g.*, sodium warfarin, digoxin, propranolol, and carbamazepine).

PRACTICAL DIFFERENCES BETWEEN TABLET AND CAPSULE DOSAGE FORMS

Solid oral dosage forms are the most widely used of all forms of medication because they offer convenience, easy and safe administration, stability, and precise reproducible dosing. They are also very well suited to mass production methodologies and

Figure 7–1. An example of uncoated compressed tablets that are scored so that they may be easily broken in half for dosage flexibility. (Courtesy of Squibb)

as a result, are comparatively less expensive to prepare. This does not apply, however, to sustained release or other controlled and extended-release products which may be relatively expensive.

Tablets are even better suited to efficient mass production techniques than are capsules. Modern high-speed tablet machines are able to produce tablets at a rate of over 10,000 tablets per minute, while capsules can usually be mass produced at only a fraction of that speed. On the other hand, in formulating dosage forms, there are fewer steps involved in capsule preparation than with tablets. Hard-shell gelatin capsules are purchased empty from an empty capsule shell manufacturer, and the only steps then involved in preparing a dosage form may be to (1) prepare the dry mix, (2) fill the capsules, and (3) polish the filled capsules. Tablet production, by either the dry-granulation or wet-granulation methods, involves a greater number of steps, although the direct compression method of tablet production involves no more steps than does capsule production.

Although both tablets and capsules can present bioavailability problems, it is likely that certain bioavailability problems that might occur with tablets can be avoided with capsules because the tablet disintegration step is not required. Once the gelatin shell disintegrates or dissolves, the capsule contents are usually released into the gastric fluids as a powder rather than as granules as in the case with tablets. However, bioavailability problems are still possible with capsules, especially if the powdered lubricants used to permit the powder mix to flow freely during the filling process result in an excess of hydrophobic properties of the powder. It is also possible to overpack capsules so that the powder remains agglomerated after the gelatin shell dissolves. However, since the contents of properly formulated and filled capsules are released as finely dispersed powder rather than as tablet fragments

or granules, capsules pose fewer problems of irritation to the gastrointestinal mucosa. Such irritation may occur if tablets, fragments of tablets, or large granules remain in contact with sensitive gastric tissue for an extended period.

Hard-shell gelatin capsules offer several advantages over compressed tablets that make them highly desirable for many patients. They completely mask unpleasant odors and tastes. They leave no aftertaste as uncoated tablets sometimes do, especially with very bitter-tasting drugs. Capsules are generally easier for most patients to swallow than are tablets. Capsules can easily be made opaque and this can offer an advantage in drugs that are photosensitive. Another advantage that capsules offer over compressed tablets is that they do not deposit powder or small fragments in the containers in which they are stored. Capsules avoid this unless they happen to come apart in the container. It must be pointed out that most advantages associated with capsules can be readily imparted to tablets by applying a coating of one type or another to the tablet—a commonly used procedure.

Whenever it is necessary for the pharmacist to prepare solid dosage forms extemporaneously, because a particular drug, combination of drugs, or a given strength of a drug is not commercially available, it is generally most convenient to employ the hard-shell gelatin capsule as the dosage form of choice. Hard-shell gelatin capsules are especially suitable for situations when the pharmacist must prepare reduced dosages of drugs that are commercially available only as prefabricated capsules or tablets of fixed strengths. In doing this it is necessary to crush tablets or empty the contents of commercially available capsules and, using suitable compounding techniques, capsules of the desired composition and potency can be prepared. When pharmacists are asked to participate in clinical trials for a new drug by providing the clinical samples for administration to the subjects, capsules are usually the best dosage form to use, unless of course, the clinical samples are already provided by the pharmaceutical company or other agency which is sponsoring the study.

Two important variations of compressed tablets and hard-shell gelatin capsules are chewable tablets and soft-shell gelatin capsules. Although they are less commonly used forms of tablets and capsules, they are both popular and offer some unique flexibility in the area of solid dosage forms. Chewable tablets combine the convenience and stability of tablets with the ease of swallowing that oral liquids allow. Although mainly intended for pediatric use, they are also helpful for adults and especially for geriatric patients who may have difficulty in swallowing tablets. With the desirable features of mannitol as a tablet base and the application of flavoring techniques, excellent palatability may be achieved. In the use of antacid tablets, chewable forms are primarily intended to improve the efficacy of the antacid medication. However, ideally, antacids should be administered as a liquid to provide more rapid relief of hyperacidity.

Soft-shell gelatin capsules are generally easier to swallow than hard-shell capsules, but the primary reason they are employed is to contain liquid or thick suspension forms of medication. The shells are composed of gelatin with glycerol or polyhydric alcohols and other additives to supply plasticity. The technology involved in their preparation is relatively sophisticated and they are supplied through a relatively limited number of sources. The liquids enclosed in these types of capsules must not contain more than 5% water, and may be clear liquids as in the case of vitamin A, vitamin D, and vitamin E, or pasty suspensions as in the case of multiple vitamin preparations.

FACTORS AFFECTING DRUG ABSORPTION FROM SOLID ORAL DOSAGE FORMS

For drugs to be effective when administered as solids by the oral route, at least three sequential processes must be completed—namely disintegration or deaggregation, dissolution, and absorption. As reviewed in detail in Chapter 4, there are several physicochemical and physiologic factors that can alter these processes.

Failure of a tablet to disintegrate or dissolve is a limitation sometimes incurred with the oral route. The physicochemical properties that control dissolution and disintegration are related to properties of the drug and excipients used, the formulation and formulation approach, various dosage form properties (such as density, hardness, and porosity), and to various interactions of all these effects; and the expertise of the dosage form manufacturer. It is the responsibility of the pharmacist, the drug manufacturer, and the drug regulatory agency to ensure that the drug product will disin-

tegrate and dissolve properly, thus providing adequate bioavailability. This responsibility has become increasingly important as more and more generic products appear and as the pharmacist plays an increasing role in drug product selection. Other factors potentially affecting disintegration and dissolution include the time of administration (with or without food and the nature of any food present in the gastrointestinal tract), physiologic factors, disease states, and so forth (see Chap. 4, Basic Concepts in Biopharmaceutics, and Chap. 5, Patient Factors that Influence Dosage Form Selection for more detail).

The volume of fluid in the gastrointestinal tract determines the volume of dissolution medium available for oral dosage forms to undergo disintegration and dissolution. For this reason it is essential that these forms of medication be ingested with water which, of course, is necessary to enable most patients to swallow the tablet or capsule. The volume of fluid ingested with the drug has been shown to alter absorption characteristics in some cases. Newborn infants have a stomach fluid content of only about 1 ml/kg of body weight.

LIQUID ORAL DOSAGE FORMS

SYRUPS AND ELIXIRS

Essentially all of the various classes of liquid pharmaceutical dosage forms that may be used for oral medications may also be prepared as delivery systems for medications which are intended for topical or parenteral administration. Syrups and elixirs, however, represent dosage form categories that are intended exclusively for administration by the ral route because, by definition, they are both sweetened and flavored. Syrups and elixirs also have other characteristics in common. Both are true solutions in the physicochemical sense. Both are usually pleasant tasting forms of medication, demonstrate excellent chemical, physical, and microbial stability, and may be stored at room temperature for relatively long periods of time. In fact, it is sometimes difficult to distinguish between elixirs and syrups, and occasionally the choice of a designation for a sweetened, flavored oral liquid dosage form is somewhat arbitrary, with either a syrup or elixir title being acceptable.

Syrups are classically defined as concentrated sucrose solutions which contain flavors. The base for many medicated syrups is a nearly saturated sucrose solution which consists of 85 g of sucrose per 100 ml of total solution, and is referred to as "simple syrup" or "syrup" USP/NF. Because simple syrup is nearly saturated with respect to sucrose, cold temperatures may bring about the crystallization of syrups. The specific gravity of simple syrup is 1.31. Therefore, 100 ml of simple syrup weighs 131 g, of which 85 g is sucrose, and the balance (46 g) is water. To prepare 100 ml of the syrup, 46 ml of purified water is heated to incipient boiling, preferably in a water bath, and 85 g of sucrose is incorporated with continuous stirring until complete dissolution is effected. The resultant syrup should then be removed—at once—from the source of heat to minimize discoloration from heat degradation. Extemporaneously prepared syrups are not filtered through filter paper because, due to their high Newtonian viscosity, the process would be too time consuming. Instead they are strained through gauze or cotton. Clarification of industrially prepared syrups is usually achieved using batch-pressure filtration equipment like the filter press.

The fact that pharmaceutical syrups generally show good microbial stability might seem surprising, since dilute sugar solutions provide a suitable growth medium for the multiplication of yeasts, molds, and bacteria (as evidenced by visible turbidity, fermentation of the sugar, and changes in the odor, taste, and appearance of the product). Nearly saturated solutions of sugar in water, however, because they are strongly hypertonic, retard most of this harmful microbial growth, and simple syrup requires no antimicrobial preservative if it is prepared and stored properly. Several other syrups do not require a preservative for similar reasons. However, if the sucrose concentration falls much below 80% (weight–volume) then a preservative to inhibit microbial growth must be added. Some useful preservatives for syrups as well as elixirs, together with their usual concentrations, are as follows:

Benzoic acid	0.1%
Sodium benzoate	0.1%
Methylparaben	0.1%
Propylparaben	0.05%
Sorbic acid	0.1%

Some syrups contain alcohol, which is usually incorporated to aid in the solubilization of a flavor

alcohol in syrups rarely exceeds 5%, no preservative effect from the alcohol would be expected. Sometimes sugars other than sucrose are used to prepare syrups. For example, in the preparation of the expectorant hydriodic acid syrup, dextrose is used instead of sucrose to achieve better chemical stability. Sucrose in solution can be hydrolyzed to D-glucose (dextrose) and fructose (levulose). The reaction is catalyzed by a small amount of hydronium or by heat. This reaction is actually the first step in the fermentation process, and an undesirable occurrence in syrups. The presence of levulose is associated with a darker color in syrups, and levulose is responsible for the amber color of simple syrup.

The preparation of syrups by solution with heat, as described for simple syrup, may be employed when the various constituents are neither volatile nor heat labile. It is also possible to incorporate the sugar and other components into a syrup without the use of heat. However, mixing or some other suitable form of agitation is required, and this method is much more time consuming than when heat is used. This is even true when the cold agitation process is carried out in the large mixing tanks used in the pharmaceutical industry. This method is not particularly suited to achieving near saturation with respect to sucrose. Sometimes medications are added to already-prepared syrups. This is a useful technique since the drug component of a syrup is often the most heat labile. When drugs in powdered or crystalline form are to be incorporated into a flavored syrup base, it is essential that the drug first be dissolved in a small quantity of water rather than trying to place it directly into the syrup itself. The viscid nature of syrups, and the fact that many of them approach saturation with respect to sugar makes it difficult to dissolve powdered or crystalline drugs directly into them. Pharmacy practitioners must remember this approach whenever a prescription calls for the incorporation of codeine phosphate, ammonium chloride, or similar substances into a syrup.

The most important medicinal syrups cover a wide range of therapeutic categories, but among the most frequent categories are antihistamines, antitussives, expectorants, and antipsychotics–sedatives. Some of the commonly used syrups may be reviewed by examining the current *United States Pharmacopeia* (*USP*) or *National Formulary* (*NF*) (see index under Syrup.) However, there are many widely used important commercially available prescription products, particularly combination products, which are not recognized as compendial syrups.

For example, combinations of antihistamine and decongestants are widely used in syrup form In most cases, the commercially available syrup dosage forms have solid dosage form counterparts

The potency of syrups is usually expressed in terms of mg per 5 ml, and the dose delivered by 5 ml is usually less than the dose delivered by tablet or capsule. This enables the syrup dosage form to be adapted to the needs of the pediatric patient as well.

Elixirs, like syrups, are brilliantly clear, flavored solutions which have been sweetened with sucrose, other sugars, or sweetening agents like the polyhydric alcohols, saccharin, or other substances. Elixirs differ from syrups in that they always contain alcohol. The alcohol present in elixirs is intended to provide cosolvent effects, and the choice of an elixir dosage form is generally made when a particular drug exhibits improved solubility characteristcs in a hydroalcoholic vehicle as compared with a strictly aqueous vehicle. The most commonly used elixirs may be reviewed by examining the current *USP* or *NF* (see index under Elixirs). The alcohol content of elixirs officially recognized in the *USP* or *NF* varies from a low of 2.7% to a high of 44%. Although elixirs which contain less than 5% alcohol are somewhat difficult to distinguish from syrups, elixirs are generally less viscid than syrups because they contain less sugar and are usually less sweet. Also, the elixirs usually contain a cosolvent in addition to alcohol such as glycerin or propylene glycol, which may also contribute sweetness to the preparation. Frequently incorporated into modern elixir formulations is 70% sorbitol solution. This is added for sweetness as well as for the other advantages of sorbitol, but simple syrup is also used in some elixirs as the sweetening agent. Like those syrups containing less sugar, certain elixirs containing less than 10% alcohol require the addition of antimicrobial preservatives (elixirs which contain over 10% alcohol and volatile oils, as flavoring components, are self-preserving). Elixirs provide stability properties at least as good as syrups and may be stored at controlled room temperature.

The USP/NF formula for terpin hydrate elixir illustrates a traditional elixir formulation:

Terpin hydrate	17 g
Sweet orange peel tincture	20 ml
Benzaldehyde	50 μl
Glycerin	400 ml
Alcohol	430 ml
Syrup	100 ml
Purified water to make	1000 ml

This elixir contains a relatively high concentration of alcohol in the solvent system in order for the terpin hydrate to remain in solution. The presence of glycerin as a cosolvent also facilitates the solubility of terpin hydrate, and if the glycerin were not included in the formula, an even higher concentration of alcohol would have to be employed in rder in order to keep the drug in solution. Since terpin hydrate is not water soluble, the crystals are dissolved in the alcohol when preparing terpin hydrate elixir, with the nonalcoholic liquids being incorporated last. Attempts to dilute terpin hydrate elixir and related elixirs such as terpin hydrate and codeine elixir with aqueous liquids such as cough syrups may cause an immediate or gradual precipitation of terpin hydrate crystals. If it is necessary to dilute terpin hydrate elixir, or for that matter other elixirs, it is a good idea to incorporate enough additional alcohol, glycerin, or propylene glycol, so that the final concentration of these solvents in the preparation is the same as their concentration in the original elixir. In this way any solubility problems causing drugs to crystallize out of solution may be avoided.

Other implications of using elixirs as pharmaceutical vehicles are represented by phenobarbital elixir USP:

Phenobarbital	4 g
Alcohol	150 ml
Orange oil	0.75 ml
Glycerin	450 ml
Amaranth solution	10 ml
Syrup	150 ml
Purified water to make	1000 ml

If dilution with vehicles having lower concentrations of alcohol or glycerin occurs, phenobarbital-free acid may precipitate out. In the case of this elixir, it is also important to avoid using diluents that will alter the *p*H from that of the original elixir. If the *p*H is lowered, a greater proportion of phenobarbital will be converted to the free-acid form and the likelihood of drug precipitation will be increased. On the other hand, if the *p*H is increased, there will be less probability of problems arising due to the precipitation of the free-acid form of phenobarbital, but the chemical stability of phenobarbital may be compromised if the *p*H becomes too alkaline.

The formula for the flavoring elixir, aromatic elixir is as follows:

Orange oil	2.4 ml
Lemon oil	0.6 ml
Coriander oil	0.24 ml
Anise oil	0.06 ml
Syrup	375 ml
Talc	30 g
Alcohol and Purified water, each, a sufficient quantity to make	100 g

This formula illustrates the use of talc as a general filtering aid in the clarification of elixirs. The volatile oils, being alcohol-soluble components, are dissolved in sufficient alcohol to make a total volume of 250 ml. The syrup and water are then added and the talc is mixed in. The resultant product is filtered through paper that has been previously wetted with diluted alcohol NF. The filtrate is collected and recycled through the same filter paper until a clear filtrate is attained. The talc functions to adsorb excessive undissolved volatile oils which could cause cloudiness in the elixir. Like syrups, elixirs generally have their dose expressed in terms of units per 5 ml, and the doses per 5 ml are frequently less than the dose of the same drug would be per solid dosage form. Modern elixirs tend to have lower alcohol concentrations, and usually, although not always have solid dosage form counterparts.

ORAL SOLUTIONS AND AROMATIC WATERS

Oral liquids that are true solutions in the physicochemical sense, but are not specifically classified as elixirs or syrups, and do not contain a substantial amount of alcohol, are likely to fall into the category of oral solutions or aromatic waters. Aromatic waters are clear, saturated solutions of volatile oils in water. Peppermint water NF is one of

the best known examples of an aromatic water that is used orally, either as a vehicle for other drugs, or as a carminative. Although aromatic waters may be prepared by the distillation of water containing the aromatic substance, the pharmacy practitioner generally uses the simple solution method. This method involves shaking 2 ml of the volatile oil (or 2 g if a solid substance is involved) with 1000 ml purified water repeatedly during a 15 minute period, allowing the resultant mixture to stand for 12 hours, followed by filtration through wetted filter paper, and adjustment of the filtrate to volume by adding sufficient purified water through the filter to make 1000 ml. The incorporation of 15 g of talc or another suitable filtering aid dispersing medium may speed up the process considerably.

Because aromatic waters are saturated with respect to the volatile component, they are subject to the salting-out effect that causes the volatile oil to separate out when strong electrolytes are added. This poses some problems if certain salts are incorporated into a vehicle which is an aromatic water. However, this problem may be overcome by filtering the finished product.

Oral solutions make up a relatively large group of products as can be seen from a review of the listing of the official oral solutions in the *USP* or *NF* (see index under solutions). Oral solutions are closely related to syrups and elixirs but they do not always meet the specific definitions of those classes of dosage forms. They are usually aqueous solutions in the same sense that syrups or elixirs are, although there are exceptions as in the case of ergocalciferol oral solution, a nonaqueous solution in propylene glycol. The majority of oral solutions are more concentrated forms of liquid medication than are syrups and elixirs. These are referred to as oral concentrates and are usually intended to be administered in volumes of less than 5 ml and frequently in doses as small as 1 or 2 drops. Oral liquid concentrates are usually sweetened, but not to as great a degree as syrups. They may also be sugar-free, with saccharin as a sweetener. They tend to contain the same kinds of components as syrups and elixirs and the same formulation principles apply.

The oral solution concentrates are usually not intended for direct administration, but are intended to be diluted with water, fruit juices, milk, other beverages, or foods. Because of the smaller volumes that need to be administered, the medication can sometimes be given in an unobtrusive manner. It is imperative that the pharmacist always recognize oral liquid concentrates and not mistake them for a conventional oral solution with a 5-ml dose.

Some oral solutions are made available in the form of powder mixtures for reconstruction into oral solutions, usually because the drug exhibits only limited chemical stability in solution form. Frequently, the cause of this limited stability is a hydrolytic degradation reaction. The penicillins are a particularly good example of this type of oral solution. In the case of the penicillin solutions drug degradation occurs by first-order kinetic hydrolysis, and it has been found that various generically equivalent brands of oral penicillins for solution may differ in the rates of penicillin degradation, apparently because of formulation differences. Such formulation differences may involve buffers, flavoring or sweetening agents, and preservatives. Official solutions that require reconstruction by the pharmacist at the time of dispensing are found in the current *USP* or *NF* (see index under Oral Solutions). These powdered or granular mixtures may be reconstituted into solution by merely adding the volume of purified water that is specified by the manufacturer's instructions given in the package literature. In general, patients should be advised to store these reconstituted solutions in the refrigerator, and that their stability is such that they should be discarded after one or two weeks following reconstitution. The majority of these solutions are antibiotics.

SPIRITS AND TINCTURES

Both spirits and tinctures represent dosage form classes that involve alcohol, either for solubilization purposes, or to extract active ingredients from plant components. The concentrations of alcohol involved in these preparations are higher than one finds in elixirs or syrups. It should also be noted that both spirits and tinctures may be used as either internal or external liquids. As classes of dosage forms, they were more widely used in earlier times. However, there are still a few examples of these dosage forms that are widely used for oral administration today.

Spirits, also called essences, are alcoholic or hydroalcoholic solutions of volatile substances. The alcohol content of these preparations is usually

higher than 60%. Those spirits that are still in general use and are intended for oral administration are peppermint spirit, compound orange spirit, and camphor spirit. Both peppermint and camphor spirits are used as carminatives and are usually mixed with water before being taken. Compound orange spirit is used as a flavoring agent in elixirs and has traditionally been employed for flavoring phenobarbital elixir, although official USP versions of phenobarbital elixir may be prepared without using compound orange spirit. Compound orange spirit is simply a solution of four volatile oils (orange, lemon, coriander, and anise) in alcohol. The procedures for preparation of the official spirits are outlined in the current *USP* or *NF*.

Tinctures are alcoholic or hydroalcoholic solutions prepared by processes involving the extraction of plant materials or sometimes by merely dissolving chemical substances in solutions of high alcoholic concentrations. Tinctures that are prepared by the extraction of plant materials traditionally contain the activity of 10 to 20 g of crude drug per 100 ml of tincture. Chemical tinctures vary in strength. Although they are subject to loss of alcohol by volatilization if the containers are not kept tightly closed, tinctures are among the most stable of liquid pharmaceutical preparations. Their relatively high alcohol concentrations, which range from approximately 19% in opium tincture to approximately 80% in tolu balsam tincture, are usually sufficiently high to retard microbial growth, and they also demonstrate a remarkable degree of chemical stability. However, occasionally sediment will form in tinctures. The sediment is usually composed of inactive plant components, so that the formation of the sediment does not detract from the potency of the tincture. Such sediment may be removed by decantation or filtration. In the preparation of tinctures, there is usually an extraction process that involves the use of alcohol, and at the conclusion of the process, the tincture is adjusted to a precise alcohol concentration that is usually just adequate to maintain the active components in solution. Therefore, diluting tinctures with other pharmaceutical liquids such as solutions, syrups, r elixirs is likely to cause a precipitation of active constituents from the tincture. Such an occurrence may require some formulation change—such as an alcohol concentration adjustment.

Medicated tinctures for oral use are becoming less widely used due to their generally poor taste and the growing preference for purified active components over plant extractives. Paregoric, however, is still a widely used oral tincture and, in fact, ranked among the top twenty most widely prescribed drugs by generic name in 1979. Its continued popularity is interesting in view of its long history. Until the 1960s, it was widely available on a nonprescription basis, but since that time it has become limited to prescription status and its availability is further restricted by virtue of its status as a controlled substance. Also known as camphorated opium tincture, it is classified as an antiperistaltic and is useful in the treatment of certain types of diarrhea. It is usually administered in teaspoonful doses to adults, supplying 2 mg of morphine per 5-ml dose. Paregoric is often mixed with water or water containing sugar to improve palatability. The alcohol content is 45%, and 4% glycerin concentration is included to prevent the separation of plant constituents from the tincture. Two other medicated oral tinctures that are in general use are opium tincture and belladonna tincture. Opium tincture, also called "laudanum" or "deodorized opium tincture," contains 10 mg of morphine per ml, and is not to be confused with paregoric because it is 25 times more potent than paregoric. The doses in which both opium tincture and belladonna tincture are usually prescribed are of such small volume that the patient is frequently directed to measure the dose in drops, and the drops are usually mixed into water. These tinctures may also be used in the preparation of various compounded liquid prescriptions. There are also nonmedicated oral tinctures that are used as flavoring agents, especially in the preparation of other pharmaceutical liquids such as elixirs. Examples are sweet orange peel tincture, tolu balsam tincture, and vanilla tincture.

ORAL LIQUID DISPERSIONS

The oral liquids described in the preceding sections have been, from a physicochemical point of view, true solutions. However, there are also important groups of oral liquids that fall into the category of coarse dispersions. Because the oral liquids that fall into this category are heterogeneous systems rather than single-phase homogeneous systems, their most obvious characteristics from a pharmaceutical point of view are their opacity and their

to ensure that ingredients are uniformly distributed so that a uniform dose of medication is achieved from a given volume of liquid. Depending on the particular flow of properties the liquid, shaking may also facilitate the pouring process.

Oral liquid dispersions are generally classified as either suspensions or emulsions. Oral liquid emulsions are rather limited now in therapeutic applicability, but oral suspensions are very popular as can be judged from the rather extensive listing of important oral suspensions included in the current *USP* or *NF* (see index under Suspensions). While both oral suspensions and emulsions are dispersed systems in which the dispersion medium is a liquid, the primary difference between the two preparations is that the dispersed phase for suspensions is a solid, while the dispersed phase for emulsions is a liquid. In both cases, of course, the dispersed phase and the dispersion medium are immiscible.

Oral Suspensions

Oral suspensions are relatively coarse dispersions in which the particle size distribution of the dispersed phase includes many particles that are considerably beyond the colloidal size range. Therefore there is a tendency for those dispersed particles, which are of a median diameter in excess of 0.5 μ (1 μ = 10^{-3} mm), to settle out from the suspension. Particle sizes in an oral suspension are large enough not to undergo diffusion and are filterable using ordinary filter paper. Like other oral liquids, such as syrups and elixirs, oral suspensions are usually sweetened and flavored and may contain antimicrobial and other types of preservatives. In addition, suspensions may contain suspending agents and other excipients designed to prevent excessive sedimentation, caking or flocculation, and to allow easy dispersibility and flow.

There are several reasons why certain drugs are suitable for use in the form of oral suspensions. These include solubility, stability, pharmacokinetic modification, and palatability. Some drugs are not sufficiently soluble in conventional, safe and legally permissible vehicles (*e.g.*, water, syrup, hydroalcoholic mixtures, water/glycerin blends) to provide the desired dose in a 5 to 15 ml volume. For drugs that undergo hydrolytic degradation or other forms of chemical instability, the suspension form frequently offers an opportunity to prepare a product with long-term stability that would otherwise not be possible in a liquid dosage form. Chemical stability is often improved if the drug is insoluble in the liquid medium. For this reason, suspensions may be prepared with a water-insoluble derivative of the parent drug. The insoluble derivative may be an ester, as in the case of acetyl sulfisoxazole, or an insoluble salt, as in the case of propoxyphene napsylate. Sometimes the drug itself is sufficiently insoluble so that a suspension may be prepared without derivatization, as is the case of phenytoin in which the free-acid form of the drug (as opposed to the sodium salt) is sufficiently insoluble so that an aqueous suspension may be prepared. Similarly, the fact that in aqueous suspensions the relatively insoluble drug greatly reduces or eliminates taste sensation permits the formulation of palatable oral liquids which would otherwise not be possible due to the bad taste of certain drugs. Pharmacokinetic modification achievable with suspension forms relates essentially to improved absorption properties. Suspension forms of drugs may be more readily bioavailable than comparable capsule or tablet solid dosage forms because the initial disintegration step is bypassed. On the other hand, oral homogeneous solution dosage forms present even less bioavailability problems than do oral suspensions because they do not involve the dissolution step which is a necessary prerequisite to the absorption of drugs administered in suspension form. Significant bioavailability differences among generically equivalent brands of oral suspensions have been occasionally observed.

Suspending Agents

The need for inclusion of one or more suspending agents among other excipients distinguishes suspensions from other oral liquids. The suspending agent(s) impart several important and desirable characteristics to a suspension. Suspending agents reduce the rate at which particles settle out. The rate of sedimentation can be decreased by increasing the viscosity of the dispersion medium, and suspending agents frequently act, at least in part, by this mechanism. Particle size and particle density in relationship to the density of the dispersion medium are also determinants of the sedimentation rate of suspended particles as predicted by Stokes' Law which applies to spherical particles:

$$v = \frac{2r^2(\rho - \rho_o)g}{9\eta_o} \qquad (7\text{-}1)$$

where v is the velocity of sedimentation; r is the radius of the spherical particle; ρ is the density of the suspended particle; ρ_o is the density of the dispersion medium; g is the gravitational constant (acceleration due to gravity); and η_o is the viscosity of the dispersion medium. Control of particle size is one technique that formulators of suspensions use to control the rate of sedimentation.

Suspending agents can, in addition to altering the viscosity of the dispersion medium, also coat the individual particles of the suspension, thus controlling the amount of flocculation and clumping of dispersed particles. Excessive flocculation is undesirable because floccules, or groups of suspended particles loosely joined together by weak van der Waals forces, may lead to an excessively rapid rate of settling. By controlling the extent of flocculation and sedimentation, excessive caking may also be avoided. Caking refers to a phenomenon whereby sedimented particles at the bottom of a suspension pack together so that the suspension cannot easily redisperse upon gentle shaking. The suspending agent influences another important aspect of suspensions—their rheological properties. Rheological properties of suspensions refer to their flow characteristics. In general, the addition of suspending agents to suspension systems tends to impart the rheological property of pseudoplasticity. Pseudoplastic flow means that as shearing stress, which may be compared with force of agitation or shaking, is intensified, the system flows more readily in comparison to the rate of flow that might be predicted proportionally at lower shearing stresses. This is a beneficial property in suspensions in that it favors easier flow and possibly easier redispersion whenever shaking occurs. Another flow property that can be influenced by the choice of suspending agent is thixotropy. Thixotropy in a liquid system means that a gel-like nature may result in certain systems upon standing. As a gel-like or latticelike network is formed in the system, sedimentation is impeded. Upon shaking, however, the gel-like property is reversed, allowing for flow. These properties are important in suspensions because they relate to settling-out properties and flow properties thus influencing redispersibility and easy pourability. For further review of physicochemical factors pertaining to viscosity and suspending agents, see discussion in Chapter 3.

A few materials that are commonly used as suspending

Table 7–4. Some Commonly Used Suspending Agents

SUSPENDING AGENT	USUAL CONCENTRATION
Acacia	10%
Bentonite	6%
Carboxymethylcellulose* (sodium salt)	1–3%
Methylcellulose*	1–7%
Sodium alginate	1–2%
Tragacanth	1–3%
Veegum	6%

* The specific concentration of carboxymethylcellulose (sodium salt) (CMC) or methylcellulose (MC) varies depending upon the particular grade of the suspending agent which is employed. For example, MC is available in several different viscosity grades, designated by a centipoise (cps) number, which is a unit of viscosity. MC 4000 would be a suitable suspending agent in approximately 1% concentration, while MC 400 would require from 3 to 5%.

In formulating suspensions, the suspending agent must be chosen carefully because it can affect dispersibility, pourability, palatability, stability, and bioavailability of the finished oral suspension. Occsasionally surfactants may be included in the formulation to augment the actions of specific suspending agents by altering the interfacial tension between the suspensoid phase and the dispersion medium. If surfactants are employed, they too must be chosen carefully after examining their compatibility with the total suspension system being formulated, including the suspending agent which is to be used. The concentration and type of soluble electrolytes present in the suspension system can be a factor, because the electrostatic charges associated with the dispersed particles influence particle to particle interactions which in turn affect sedimentation rate and flocculation.

Preparation of Suspensions

The actual technique of preparing suspensions is somewhat more complicated than for preparing homogeneous solutions just as the formulation variables, as described above, are more complex than for syrups, elixirs, and other true solution forms. In general, suspending agents such as those listed in Table 7-4 are not readily incorporated into liquid systems by simple addition. Most of them form either single-phase or two-phase colloidal

into aqueous systems. Bentonite and veegum are suspending agents which, when incorporated into water, form two-phase systems called magmas or milks. Magmas are aqueous dispersions of small inorganic particles which become hydrated to form an inorganic gel in which there is a lattice structure consisting of discrete particles in a heterogeneous system. Magmas differ from gels only in that the size of the dispersed particles are somewhat larger. However, both gels and magmas usually have smaller particle sizes than suspensions. Bentonite, which is a colloidal, hydrated aluminum silicate, when dispersed in water, forms a magma which is highly thixotropic. The marked thixotropy that bentonite imparts to aqueous systems is an important determinant of its properties as an excellent suspending agent.

When using bentonite powder as a suspending agent, it is necessary to prepare a magma by sprinkling the powder, in divided portions, on hot purified water without stirring. After the system stands undisturbed for 24 hours, water is added to bring the system to the desired volume with stirring. The process may be hastened considerably by using a mechanical blender. The quantity of bentonite powder that is to be contained in the total volume of suspension is added to a quantity of hot water approximately equal to half the volume of the total suspension formulation. Preferably, the powder should be added while the blender is running. After 5 or 10 minutes of blending, a relatively thick magma is obtained. A magma, prepared either by the mechanical mixing process or the slower "sprinkling" technique, may be used in the formulation of the drug suspension by suitably wetting the insoluble drug powders to be suspended, with portions of the magma added separately. If this is to be accomplished without the use of a mechanical blender, as may frequently be the case in the extemporaneous preparation of small volumes of suspensions, the insoluble powders to be suspended should be first wetted with a small quantity of the magma and gradually worked into a smooth paste. After a smooth paste has been formed, gradual dilution with the magma vehicle and incorporation of flavoring agents, sweetening agents, dyes, and preservatives may occur. For large-scale processing, tank mixers and homogenizers may be used to facilitate the preparation of suspensions. These may produce smoother, more uniform suspensions, with reduced particle size.

The procedures for the use of the complex carbohydrate gums and cellulosic polymers such as sodium alginate, methylcellulose, sodium carboxymethylcellulose, and tragacanth are somewhat similar to the technique employed for the clay-type agents like bentonite. The initial process of hydration must be accomplished by sprinkling the materials on the surface of hot water and allowing hydration to occur without stirring (because stirring leads to the formation of clumps of gumlike material). Then after hydration occurs, a mucilage (also called a jelly) is formed. It may be desirable to strain the mucilage through gauze to eliminate any clumps. However, this should be done prior to the incorporation of the insoluble drug to be suspended because finished suspensions are never strained or filtered. As with bentonite, the process of hydration for the gumlike suspending agents may be hastened with the use of high-speed mechanical blenders. Initial hydration of colloids can be affected more rapidly by using hot water, even in the case of methylcellulose which is actually more soluble in cold water than in hot. These gumlike, colloidal suspending agents differ from bentonite in that they form homogeneous, single-phase colloidal solutions. The gum suspending agents add pseudoplasticity and often some degree of thixotropy, thus providing the rheological characteristics that are generally desirable in suspension dosage forms. In addition, these suspending agents increase the viscosity of the dispersion medium, thereby reducing the sedimentation rate. Acacia does not increase the viscosity of the dispersion medium except in very high concentrations and is therefore not well suited as a suspending agent.

It has been noted that suspensions are dispersions of insoluble, finely divided particles dispersed in a liquid medium which, in the case of oral suspensions, is generally an aqueous system. Oral suspensions are usually considered to be relatively coarse dispersions since the particles range in size from colloidal dimension (0.5μ) to upper limits which vary considerably, and may be as large as 100 μ in particle diameter. Some commercially available suspensions are micronized so that the suspended particles are within the microsize range, generally measuring below 10 μ. Griseofulvin is a good example of a micronized oral suspension in which particle size reduction significantly increases absorption, and thus blood levels achievable from the administration of a given dose of

drug, because the smaller particles undergo dissolution more readily.

When particle size distributions in a given dispersion fall, for the most part, within or near the colloidal range, the particles are less likely to undergo rapid sedimentation, thus the presence of suspending agents may not be as necessary. *Gels* and *magmas* are terms that historically have been used to designate certain suspensions of inorganic substances in which the particle sizes are small nough to have adequate self-suspending properties. Therefore, it is not essential to include a suspending agent in these formulations. The magmas (or milks) are distinguished from the gels in that their suspensoid phase consists of particles of somewhat larger size. Although the magmas and gels are closer to the colloidal particle size range than are the ordinary oral suspensions, they are not true colloidal dispersions and they are, therefore, still "shake preparations." Consequently it is necessary that patients be advised to shake these dosage forms before pouring out a dose—both to ensure uniform distribution of the drug in the dosage unit and to facilitate flow since these preparations tend to be thick suspensions of a thixotropic nature. The term gel is also sometimes used to refer to organic hydrocolloid jellies (mucilages) that are popularly used as the base for a number of modern dermatologic semisolid dosage forms. The inorganic gels and magmas, in contrast to the mucilages or jellies (the dermatologic gels) are heterogeneous systems.

The inorganic magmas and gels have been widely used as oral, nonabsorbable antacids for many years. The most widely used magma is milk of magnesia. Milk of magnesia is a suspension of $Mg(OH)_2$, and is frequently flavored, usually with 0.05% peppermint oil. Milk of bismuth or bismuth magma containing a combination of insoluble bismuth compounds is less widely used than milk of magnesia.

Aluminum hydroxide gel USP and aluminum phosphate gel USP are closely related in appearance and therapeutic category to alumina and magnesia oral suspension and Magaldrate oral suspension. Aluminum hydroxide gels, the best known is Amphojel (Wyeth), may contain peppermint oil, glycerin, sorbitol, sucrose, saccharin or other similar flavoring agents, sweeteners, antimicrobial preservatives, and other excipients. In appearance, aluminum hydroxide gel is a white viscous suspending agent, although it may separate slightly on standing. Although it contains the equivalent of only 4% of aluminum oxide, it is the high degree of hydration of the small suspended particles which gives these systems their thick appearance and viscous thixotropic character. Aluminum phosphate gel is best known under the trade name Phosphaljel (Wyeth). Like the oral suspension antacids, the antacid gels are superior in therapeutic effect to tablet forms of these drugs.

While the vast majority of oral suspensions are dispersions of solid particles in aqueous vehicles, it is possible to have oral suspensions in nonaqueous systems such as vegetable oils. Methenamine mandelate oral suspension USP is an example of such a suspension in which the liquid medium is a vegetable oil. While such suspensions may not be as palatable as aqueous suspensions, the stability of certain compounds may be enhanced by use of a nonaqueous vehicle.

Another technique, which may be used for suspensions of drugs with limited stability in the presence of water, is to prepare the suspension in the form of a mixture of dry powders or granules which contain all of the active drug and excipients necessary to form the suspension. At the time of dispensing, the pharmacist adds the appropriate volume of purified water to the powders to reconstitute the suspension. Examples of some common suspensions which are reconstituted in this manner are listed in the current *USP* or *NF* (see index under Oral Suspensions). After reconstitution, such suspensions usually have limited stability—two weeks or less and frequently require refrigeration.

As a result of advances in formulation technology, a manufacturer may be able to improve the stability of a liquid suspension formulation sufficiently to make it available in the form of a suspension product that does not require reconstitution. Such changes occur occasionally as a normal result of a manufacturer's ongoing product improvement program which is carried out by the pharmacy research and development group. Erythromycin estolate and erythromycin ethylsuccinate are examples of suspensions that were formerly available only as products for reconstitution, but are now available as liquid suspensions and as powders for reconstitution. In the case of these two drugs, however, the preformulated liquid suspension forms require refrigeration.

pension was available for many years only in a form that required reconstitution. Currently it is available on a multisource basis in a form that requires neither reconstitution nor refrigeration. Cholestyramine is an example of a product that comes in powder packets that are reconstituted into suspension form by the patient just prior to taking the medication. This is done by sprinkling the powder over water or another appropriate beverage and stirring.

Suspensions as Oral Dosage Forms

Suspensions as oral dosage forms offer many advantages in terms of stability, palatability, and ease of use. They are generally efficacious dosage forms from a bioavailability standpoint, although careful formulation and testing for correlation between dissolution properties and *in vivo* bioavailability are important. Although suspensions do not exhibit inherent antimicrobial preservation properties, the addition of suitable quantities of common antimicrobial preservatives can usually eliminate microbial instability problems. From the formulator's point of view, suspensions are also useful in that they permit the efficient incorporation of drugs that might be too bulky to formulate into a convenient solid dosage form or that might require too large a volume of solvent to provide a suitable dose in a true solution (syrup or elixir) oral dosage form. This is certainly illustrated in the case of theophylline in which elixir dosage forms may require a volume of 15 ml to provide a dose of drug that might be provided by just 5 ml or less of a suspension dosage form. All of these advantages account for the current widespread popularity of suspensions as commercially available forms of oral prescription and nonprescription medications.

On the other hand suspensions do cause the formulator some concerns in terms of potential physical instability problems such as settling-out, flocculation, caking, and pourability problems that are not encountered with true solutions. As pointed out, these problems can generally be overcome by the inclusion of suitable suspending agents, dispersing agents such as surfactants, and by controlling the particle size of the dispersed drug and the electrolyte content.

Oral suspensions can also be prepared extemporaneously by the pharmacist, using some of the commonly available suspending agents, whenever it is necessary to do so. Extemporaneously prepared suspension dosage forms are frequently useful whenever a liquid dosage form of a drug, which is commercially available only in the form of tablets or capsules, is required. This situation occurs not uncommonly, for new drugs as well as for experimental drugs. Even when the best possible formulation and compounding practices are employed, however, the pharmacist must recommend that such extemporaneously prepared suspensions be limited to use within a relatively short period of time after preparation unless evidence is available to justify the assumption that longer-term stability exists.

EMULSION DOSAGE FORMS

Emulsion dosage forms are by no means limited to the oral route of administration. Neither are they limited to liquid forms. Emulsions may be either liquids or semisolids. Semisolid emulsions, which are used extensively as bases for dermatologic dosage forms, are referred to as creams. In addition to their frequent use as vehicles for dermatologic drugs, emulsions may be administered by the parenteral route, and are also available as oral liquid dosage forms. However, oral liquid emulsions are not as widely used as they were in the first half of this century. In fact, their use as oral liquids is limited to a relatively few therapeutic categories. Thus the practicing pharmacist is not usually called upon to formulate or prepare such oral products. Mineral oil emulsions and castor oil emulsions are still commonly used, and an understanding of these oral liquid dispersions is based on some of the same concepts that apply to suspensions. In fact, the major difference between liquid suspensions and liquid emulsions is that for emulsions, the dispersed phase is a liquid rather than a solid as in suspensions.

An emulsion is defined as a two-phase system in which small droplets of one liquid (the internal phase) are dispersed throughout another liquid (the external phase or dispersion medium). Of course, the two liquids must be immiscible, and in oral liquid emulsion dosage forms, the two immiscible phases are oil and water. To stabilize such a liquid-in-liquid dispersion, a third component, an emulsifying agent, must be present. Without it, the dispersed phase will coalesce and separate layers of water and oil will form. Whenever this occurs in an emulsion, it is referred to as the breaking or cracking of the emulsion, and is regarded as an

irreversible form of physical instability. Modern emulsifying agents are usually surfactants, although carbohydrate gums, polymers, proteins, and other materials may also serve as suitable emulsifying agents. An emulsifying agent must provide sufficient protective colloidal action to maintain the dispersed droplets or globules in a state of separation from the dispersion medium. While various types of emulsifying agents act by somewhat different mechanisms, surfactants bring about and maintain emulsification by reducing the interfacial tension between the surface of the droplets and the dispersion medium.

When the external phase is aqueous and the internal or dispersed phase is oil, the emulsion is referred to as an oil-in-water emulsion. Water-in-oil emulsions have water as the internal phase and oil as the dispersion medium. Oral liquid emulsions most commonly are of the oil-in-water type because emulsions assume the taste properties of the external phase and therefore oil-in-water emulsions have better palatability. Oil-in-water emulsions also have the advantage that they may be diluted with other aqueous fluids, while water-in-oil emulsions may only be diluted with oils.

Irreversible coalescence of an emulsion (breaking or cracking) may be due to an inappropriate choice of emulsifying agent, excessive electrolyte concentration, inadequate homogenization, repeated temperature fluctuation, or a dispersion medium with too low a viscosity. It may also be due to an excessive phase–volume ratio which occurs when the proportion of one of the two immiscible phases is too large in comparison with the other. Another type of physical instability that is associated with liquid emulsions is creaming. Creaming is comparable to the phenomenon of sedimentation which occurs in liquid suspensions. In suspensions, the dispersed phase usually has a higher density than the dispersion medium and when sedimentation takes place, the dispersed particles fall to the bottom of the system. In oil-in-water emulsions, the dispersed oil droplets have a lower density than the aqueous dispersion medium, and so upward creaming occurs. In water-in-oil emulsion systems, downward creaming occurs. The creaming phenomenon may be readily reversible by gentle shaking. Creaming can be retarded, to some extent, by increasing the viscosity of the dispersion medium—a predictable consequence of Stokes' Law. Since creaming involves a close packing of the dispersed particles, it may be a first step toward irreversible coalescence. However, in properly formulated emulsions, creaming can occur without any danger of coalescence.

There are essentially three reasons why liquid emulsions are chosen as oral dosage forms. But all of the reasons are essentially based on the assumption that there is a need to administer an oil substance, such as liquid petrolatum (mineral oil), cod liver oil, castor oil, corn oil, or other vegetable oils. The most notable reason for choosing an emulsion dosage form is to improve the palatability of the oil. Oils are not very palatable when administered alone. By forming an oil-in-water emulsion, a relatively palatable preparation may be achieved. Castor oil is useful as an evacuant-type cathartic and is sometimes prescribed for patients who are to undergo a series of gastrointestinal diagnostic tests which require the evacuation of the lower bowel. Most patients find castor oil to be a very obnoxious-tasting medication. Prepared as an emulsion, however, with suitable sweetening and flavoring agents, it can be a rather pleasant-tasting preparation. Neoloid (Lederle) is an example of a commercially available castor oil emulsion. A second reason for using the oral emulsion dosage form is to prepare a single liquid dosage form involving two or more medications, one requiring an aqueous medium and the other requiring an oil phase. A prescription calling for milk of magnesia, mineral oil, and aromatic cascara fluid extract would be such an example. A third reason for employing the oral emulsion dosage form is that emulsification actually improves the efficacy of the oil being administered. Vegetable oils like corn oil, for example, may be administered for their calorific effects. Lipomul-Oral (Upjohn) is an example of such a product. It is thought that emulsification improves the absorption of vegetable oils because emulsification is the first step in the gastrointestinal absorption process for oils. In the case of mineral oil, which does not undergo gastrointestinal absorption, emulsification reduces the problem of anal leakage which can occur when plain mineral oil is administered orally. Emulsified forms of mineral oil are also regarded as more effective laxatives than plain mineral oil.

Emulsifying Agents. Emulsifying agents are not only essential to the formulation

they generally determine whether a particular emulsion formulation will be oil-in-water or water-in-oil. For oral liquid emulsions, the emulsifying agents must be nontoxic and they should ideally possess as little color, odor, or taste as possible. Frequently emulsifying agents may be used in combination in a given emulsion formulation. The various emulsifying agents are summarized as follows:

HYDROPHILIC COLLOIDS. These include the natural gums such as acacia, tragacanth, agar, chondrus, and pectin. In addition, the semisynthetic polymers, such as methylcellulose and sodium carboxymethylcellulose, may also be used. Many of these hydrophilic colloids can, of course, also serve as suspending agents. The hydrophilic colloids usually produce oil-in-water emulsions. Exceptions can occur because phase–volume ratio and order of mixing also influence whether an oil-in-water or water-in-oil emulsion is obtained even though the primary determinant of emulsion type is the emulsifying agent. Sometimes the hydrophilic colloids are used in combination as emulsifying agents. For emulsions that are formed using acacia, for example, tragacanth may be used as a viscosity-building agent. The USP formula for mineral oil emulsion illustrates the use of acacia as an emulsifying agent:

Mineral oil	500 ml
Acacia (in very fine powder)	125 g
Syrup	100 ml
Vanillin	40 mg
Alcohol	60 ml
Purified water to make	1000 ml

This formulation, which may vary in terms of the flavoring agent (vanillin) and the preservative (alcohol), illustrates a classical approach to the formulation of liquid oral emulsions using a hydrophilic colloid as the emulsifying agent. The emulsion "nucleus" is formed by mixing four parts oil, two parts water, and one part hydrophilic colloid. The colloid is dispersed into the mineral oil, and the two parts of water are added with rapid trituration in a mortar to form the emulsion nucleus. An emulsion nucleus may be diluted with appropriate materials without destroying the emulsion which has been formed. In the case of mineral oil emulsion, all of the remaining components of the formulation are incorporated into the emulsion, in divided portions, with trituration after each addition. After the preparation is brought to its final volume, it may be passed through a hand homogenizer or placed on a high-speed blender. A high-speed mixer or blender could also be used to prepare such an emulsion, and large-scale equipment of this type is employed to prepare the many commercial brands and variations of mineral oil emulsions that are available as OTC laxatives.

PROTEINS. Gelatin, egg white, casein, and other proteins may serve as emulsifying agents, and form oil-in-water emulsions. They are not extremely useful in modern pharmaceutical products because, unless they are used in combination with certain hydrophilic colloids, they form emulsions that are not thick enough. Also, they tend to deteriorate rapidly.

INORGANIC GELS AND MAGMAS. Substances like bentonite, milk of magnesia, and aluminum hydroxide gel can act as emulsifying agents by inducing emulsion formation, both by mechanical action in which the finely divided solids aid in droplet formation, and through a protective colloid effect on the droplets. They usually form oil-in-water emulsions but, depending on the phase–volume ratio, they may also form water-in-oil emulsions.

SURFACTANTS. Surfactants represent the most modern form of emulsifying agents, and combinations of these agents are usually employed to provide the appropriate hydrophile–lipophile balance (HLB) to produce either oil-in-water or water-in-oil emulsions. Nonionic surfactants, such as the polysorbate series (*e.g.*, Polysorbate 80, "Tween 80") or the sorbitan series are useful in that they form emulsions with good chemical and physical stability. The nonionic surfactant emulsifiers also pose fewer taste and toxicity problems than cationic and anionic surfactants. Frequently, a good approach to formulating an emulsion with nonionic surfactants involves blending a low HLB surfactant with a higher HLB surfactant, in the proper proportions, to provide a combined HLB for the system that will provide the desired emulsion properties. Higher HLB values, such as those provided by surfactants like polysorbate 80, tend to form the oil-in-water-type emulsions generally desired for oral liquids. The specific HLB value required for the formation of an oil-in-water or a water-in-oil emulsion depends on the oil being emulsified. An HLB of 12 will form an oil-in-water emulsion with

mineral oil, for example. The concentration of surfactant emulsifier in an oral liquid can vary considerably, and concentrations in the range of 10 to 30% of the oil phase are reasonable. When using nonionic surfactants, heat may be necessary in the preparation process and care should be exercised in not incorporating heat-labile or volatile ingredients until the preparation has cooled. As with the preparation of all liquid emulsions, mixing and homogenization using blenders or other equipment are generally useful.

All emulsion systems require the addition of antimicrobial preservatives and possibly antioxidants together with other chemical preservatives. The antimicrobial preservatives chosen should possess both antibacterial and antifungal activity. When planning the concentration of such agents, careful consideration must be given to the possibility that preferential partitioning of the agents can occur between the two immiscible emulsion phases. Because contamination and microbial growth are especially likely to occur in the aqueous phase in oil-in-water emulsions, preservatives must achieve adequate concentrations in the external phase of such emulsions. If excessive preferential partitioning into the oil phase occurs, this can lead to a problem of microbial instability. Excessive microbial growth in emulsions can lead to physical instability as well because many emulsifying agents may be degraded chemically by microbes.

SOLID ORAL DOSAGE FORMS
BULK AND DIVIDED POWDERS

When dry powdered drugs are administered in modern-day therapy, they are usually given in compressed, compacted forms (tablets), or as encapsulated powders in hard gelatin capsule shells. Formerly, however, dry powders, without any compression or encapsulation, were extensively dispensed by pharmacists for administration by the oral route, either in the form of divided powders or bulk powders. Today, powders are administered very infrequently by the oral route because of the availability of dosage forms that enable powders to be administered more conveniently, more efficaciously, and in accurate unit-doses. The disadvantages of administering powders by mouth are readily apparent. First of all, it is inconvenient. It is virtually impossible to administer dry powders without mixing them in food or beverage. Secondly, it is usually not a very palatable way of administering medications. Third, dosage accuracy is less than can be achieved with tablets or capsules because some of the dry powder may be lost in the process of administration. Finally, unless dispensed as bulk powders (possible only for nonpotent drugs) dry powders pose more dispensing problems for the pharmacist—because individual dosage packets corresponding to the prescribed dose to be administered must be prepared. While bulk powders are appropriately used as dermatomucosal medications, either as cleansing powders or douches, their use as oral medications is extremely limited. They may still occasionally be administered as antacids, laxatives, gastrointestinal adsorbents, or as nonspecific antidotes in cases of poison ingestion.

The use of bulk powders for oral administration is very limited. The primary criterion for their use is that the powder, or more commonly a mixture of powders, is not potent enough to require the kind of dosage accuracy that is achieved with capsules, tablets, or divided powders. The dose from a bulk powder intended for oral use is usually specified by a level, or a heaping teaspoonful or tablespoonful, or possibly a small measuring cup (provided to obtain the dose). Nevertheless, the dose actually delivered will vary, depending on how tightly or loosely the powders are packed at the time they are being administered. For stability reasons, bulk powders are best stored and dispensed in glass containers with tight closures. For convenience in using and administering powders, a wide-mouthed container is preferable.

For the administration of dry powdered forms of more potent drugs, divided powders have been used. The proper amount of powder is placed on a "powder paper" which may be any convenient size of rectangular paper and is generally the same type of paper that is used to avoid weighing powders directly on the pans of a prescription balance. Common paper sizes that have been used are 70 × 95 mm, 76 × 114 mm, 95 × 127 mm, and 114 × 152 mm. White bond parchment or glassine paper, a translucent, water-repellent material, is usually employed. The papers are folded in a traditional manner so that the enclosed powders will not be accidently released during storage and so that the powder papers will fit neatly into a dis-

pensing box. Folded powder papers were also known as "charts," from the Latin word *chartulae*, meaning small papers. Today, small envelopes or similar packets provide a more convenient means of dispensing divided powders, and the need to fold individual powder papers is thus avoided. In fact, a number of commercially available divided powders, such as potassium chloride supplements and cholestyramine resin, come in aluminum foil-type sealed envelopes, usually referred to as "packets." Such an enclosure provides moisture and atmospheric protection for the packet contents. The powder or granular mixtures usually contain flavoring and sweetening agents.

When the pharmacist is called upon to extemporaneously prepare divided powders, the maintenance of dose accuracy requires that the weight of powder in each divided powder dosage form be individually checked and adjusted. When doing this, it is important for the pharmacist to use a similar powder paper (or envelope or packet) as a tare weight on the right-side pan of the prescription balance. Of course, the balance must still be zeroed in for each weighing because the powder papers or envelopes may differ slightly from one another in weight. Usually the use of hard-shell gelatin capsules proves a more suitable alternative to the use of divided powders, unless the powder mixture per unit is too bulky to fit into a capsule of appropriate size, or unless the patient cannot swallow a solid dosage form. In the latter case, the use of a suspension dosage form may be the preferable alternative, unless stability considerations dictate otherwise. It should also be noted that in cases in which the divided powder dosage form is indicated because the patient experiences difficulties in swallowing a solid dosage form, the use of the hard-shell gelatin capsule for dispensing purposes is still an alternative. The patient can be directed to empty the contents of the capsule into a beverage prior to taking the medication.

Powders are intimate mixtures of dry finely divided drugs with or without excipients. Certain general properties of powders are important to the pharmacist, not just in relation to an understanding of divided powder and bulk powder dosage forms, but also in relation to an understanding of tablet and capsule dosage forms, since powders constitute the major components of tablets and capsules. Of particular interest are the particle-size distribution of powder mixtures, the comminution of powders, and the mixing of powders. Comminution refers to the reduction in particle size of solid drugs and chemicals. The reduction of larger particles may be achieved through the use of industrial equipment such as hammer mills, cutter mills, roller mills, and jet or fluid-energy mills. Coarse milling refers to the production of powders of particles generally larger than 20-mesh-screen size while fine milling results in powders with particles generally smaller than 200-mesh-screen size. Selection of a mill depends on the nature of the materials being milled and the particle-size distribution desired.

Sieves are devices with screens of various sizes that permit the passage of particles which are smaller than the screen openings. Numerical designations are given to standard sieves generally used in working with pharmaceutical powders. The sieve numerical designations as defined in the *USP* and *NF* range from No. 2 (sieve opening of 9520 μ) to No. 400 (sieve opening of 37 μ). The *USP* and *NF* also define the categories of powders by the ability of the particles to pass through sieves of various sizes. For example, a coarse chemical powder is one for which all particles in the powder mixture will pass through a No. 20 sieve (840 μ sieve opening) and not more than 60% will pass through a No. 40 sieve (420 μ sieve opening). Sieves can be used to classify powders because observing whether powders will or will not pass through sieves of various sizes provides a means to determine the particle-size distribution of powder mixtures. It also provides a means to ensure that limits are set on the range of particle sizes in a given powder. Essentially all powders used in pharmacy are made up on a distribution of particles of various sizes. While sieving is used as a means to separate powder particles based on size, it also may result in some particle-size reduction. This may or may not be a desirable consequence of sieving. Powders that only pass through sieves of larger-size openings (*e.g.*, designations lower than No. 10) are generally referred to as granules.

Porcelain and Wedgwood mortars and pestles provide an excellent means for the pharmacist to work with powders, since, by the process of trituration, both mixing and comminution may be accomplished. Trituration, as a process, refers to the mixing of powders with a mortar and pestle. In the process of trituration, pressure is applied downward on the pestle as it is moved in the mortar in a circular path while all of the fingers of one

hand are wrapped firmly around the pestle. During the process, most powders tend to cling to the sides of the mortar and should frequently be scraped form the walls of the mortar with a spatula and returned to the main powder mix for continued trituration. Glass mortars and pestles are not well suited to the trituration of powders because the smoothness of the glass surfaces do not provide enough friction to allow proper mixing and particle reduction to occur. Glass mortars and pestles are appropriately reserved for working with liquids. Colored liquids, on the other hand may permanently stain a Wedgwood mortar.

A technique that is particularly useful for mixing powders, especially when small quantities f powders are being diluted with larger quantities of other powders, is *geometric dilution*. It is a technique that should be employed whenever the pharmacy practitioner is mixing powders for any purpose, including the preparation of powdered formulations for inclusion in hard-shell gelatin capsules. In geometric dilution, the quantity of powder f the ingredient that represents the least weight of the formulation is placed in the mortar. Then the other powder (or powders) that constitute the majority of the total formulation by weight are sequentially added in amounts that approximately equal the bulk of the powder already combined in the mixture. For example, if 1 gram of a relatively potent drug is included in a powder formulation with 20 grams of a diluent, the 1 gram of drug is placed into the mortar, and then approximately 1 gram f powdered diluent is added, followed by thorough trituration. Then approximately 2 g of diluent is added, followed by thorough trituration. Then 4 g, 8 g, and so on, until all of the powders are incorporated. For powdered mixtures containing three or more ingredients, the ingredient present in the least amount is always introduced first, and the ingredient present in the greatest amount is always incorporated toward the end of the dilution process. The effectiveness of the process of geometric dilution as a mixing technique for small batches of powders using the mortar and pestle can be amply and vividly demonstrated by diluting a very small quantity of a powdered dye with a diluent such as lactose.

While the use of the mortar and pestle is adequate for the mixing of small batches of powders, such as those encountered in community and which occurs in the pharmaceutical industry requires the use of mechanized large-scale mixers. Trough mixers with rotating blades, spines, or paddles and rotating double-conical blenders (see Fig. 7-2) are common types. These kinds of mixers come in various sizes so that different size batches can be accommodated. Some are very large with mixing capacities of several hundred to several thousand pounds of powder. High-shear mixers also exist in a wide range of machine designs that function to mix powders by the same general principle of the mortar and pestle.

It was pointed out earlier in this chapter that dosage forms consisting of dry powder forms of drugs are intrinsically more stable than liquid dosage forms. This is particularly true in terms of chemical and microbial stability. However, drugs and chemicals in dry powder form can exhibit certain forms of physical instability, either during processing or throughout the life of the dosage form. Some types of physical instability may have deleterious effects on the appearance, chemical stability, bioavailability, and efficacy of dosage forms which involve powdered drugs and excipients. Some of the types of physical instability that particularly affect dry powders are hygroscopicity, deliquescence, efflorescence, volatility, and eutectic formation. Hygroscopic powders tend to pick up moisture from the atmosphere to which they are exposed. As the relative humidity in the atmosphere increases, the problem becomes more severe When so much moisture is picked up that the powder liquefies, deliquescence is said to occur. Substances that are highly hygroscopic may even extract the normal water content from the hard-shell gelatin capsules in which they are enclosed, making the capsules very brittle. On the other hand efflorescence involves a physical change of powders or crystals that contain water of hydration as part of their molecular structure. Such water of hydration may be given off in atmospheres of low relative humidity, especially at elevated temperatures, such as the higher temperatures that may be generated during vigorous trituration. Efflorescence may alter the physical appearance of such powders and may render the powders very wet. Volatility is also a problem with some drugs and excipients in powder or compacted powder forms. Nitroglycerin is an example of a drug which can volatilize, even when it is contained in a tabl

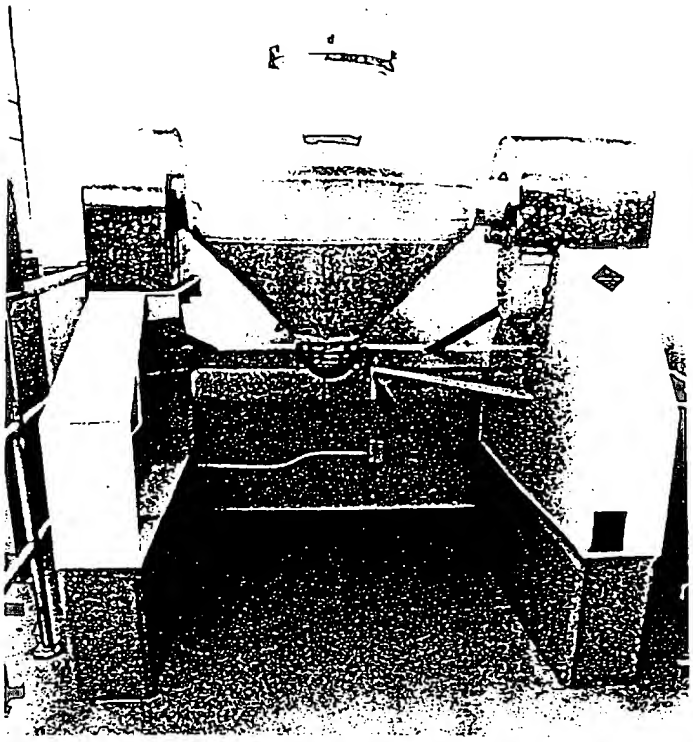

Figure 7–2. A large volume rotating blender for mixing powders. (Courtesy of Squibb)

containers or in containers with closures that are not tight enough. It is essential that drugs exhibiting these various forms of instability be protected from exposure to the atmosphere and that appropriate containers with tight closures are used.

That the presence of impurities tends to lower the melting point of an organic compound is a well-known chemical principle. It is a consequence of the same principle that certain powders of similarly low melting point or structure, may actually form mixtures that liquefy at room temperature. Such mixtures are referred to as eutectic mixtures. Chloral hydrate and the salicylates are examples of orally used drugs that commonly exhibit this phenomenon. Usually the problem of a eutectic mixture may be readily corrected by the addition of an inert powder with a high melting point and high specific surface, to the mixture. Magnesium carbonate is generally best suited, but kaolin, talcum, or magnesium oxide may also serve as protectants against eutectic formation. Each of the eutectic-forming ingredients is individually mixed with an amount of protecting agent approximately equal to its own weight. Then all of the ingredients of the powder formulation are mixed together.

HARD-SHELL GELATIN CAPSULES

Hard-shell gelatin capsules are still the most widely used form of capsules, although soft-shell elastic gelatin capsules are increasing in popularity. Hard-shell gelatin capsules are used mostly for the encapsulation of powdered drug formulations so that they may be delivered to the patient in an accurate unit-dose which is easy to swallow and devoid of any unpleasant drug taste. In addition to containing simple powder formulations, hard gelatin capsules may also be used to contain coated beads, pellets, or granules used as sustained-release forms of medication. The hard gelatin capsule may be the only

:asible dosage form for coated particles or beads sed in sustained-release formulations because ompression of such particles in a tablet would isrupt the coating. All of the discussion in the receding section on the properties of powders and ie techniques to mix powers apply to the prepaition of powder formulations for inclusion in hard elatin capsules.

An empty gelatin capsule is made up of two arts, a *base* which is designed to contain the owdered contents of a capsule dosage form, and ie *cap* which is only about one-half as long as the ase. The cap fits over the open end of the base f the capsule snugly enough to preclude the inivertent opening of the capsule during normal se, thus eliminating the possibility of losing any f the powdered contents. In some special capsules, ie cap may be sealed to the base of the capsule ith a band of gelatin that is applied with a rather ecialized type of industrial machinery after the apsule has been filled. Kapseals (Parke-Davis) rand of capsules sealed with a gelatin band, is an kample of a band-sealed capsule which offers the ivantages of a distinctive appearance, a tamperroof seal, and an assurance that the cap and the ase will not inadvertently come apart. Caps may lso be sealed on the base of the capsule by means f interlocking indentations between the base and ie cap. These various seals and locks are usually mited to capsule dosage forms of commercially anufactured pharmaceutical products, and they re not available in the hard-shell gelatin capsules sed by pharmacists in extemporaneous prescripon compounding. Some commercial product capules also have distinctive shapes, usually achieved y a special tapering effect at each end of the apsule, differentiating it from the traditional capule used in extemporaneous prescription compounding.

The two shells or parts of the capsule, the ase and the cap, are made of special blends of one and pork-skin gelatin. They may either be olorless or may contain certified colorants such s the D & C or FD & C dyes. Hard-shell gelatin apsules are either transparent or opaque. Titanium ioxide is a common opaquing agent in capsules. mpty hard-shell gelatin capsules available for use extemporaneous prescription compounding are f the transparent type and can be either colorless r pink. Commercial product capsule dosage forms ome in an impressive variety of colors, both transparent and opaque; some capsules are two-tone with the cap and base each a different shade of the same color or they may each be a different color altogther. The gelatin mixtures used to prepare hard-shell gelatin capsules may contain certain additives such as hardening agents, preservatives, and dispersing agents. In addition, these capsules possess a water content of between 10 and 15%. This water is important for it serves as a plasticizer to maintain capsule elasticity.

A heated gelatin liquid mixture is used to form the empty hard-shell gelatin capsules by a process that involves dipping metal pegs in the shape of the capsule shells into the warmed gelatin liquid, followed by an air drying process which allows the gelatin on the pegs to harden. The hardened shells are then removed from the pegs, and the caps are joined to the base by placing the cap over the open end of the capsule base. The whole procedure is carried out on large-scale, automated, and highly specialized machinery. If capsules are imprinted with a distributor's logo, a National Drug Code (NDC) number, or any other alpha-numeric characters, this is done mechanically on the empty capsules rather than after the capsules have been filled with powder. Because the composition of the capsule shells includes 12 to 15% water, the hard-shell gelatin capsules are subject to dehydration when stored in an atmosphere of low relative humidity. Excessive dehydration may cause the capsules to become brittle and to crack easily. On the other hand, exposure of hard capsule shells to excessive moisture will lead the gelatin shell to soften and even to dissolve.

There are eight capsule sizes used for oral drug administration in human medicine. Larger sizes are used in veterinary medicine. The various capsule size designations for human use, together with the usual range of powder capacity for each size are summarized as follows:

Capsule Size Designation	*Usual Range of Powder Capacity*
5	60–130 mg
4	95–260 mg
3	130–390 mg
2	195–520 mg
1	225–650 mg
0	325–910 mg
00	390–1300 mg
000	[illegible]

The reason for the large range of weights given to describe the capacity of each capsule size is that various powders differ considerably in their bulk densities and compressibilities. For example, bismuth subnitrate is a very dense powder and so a capsule of given size would be able to contain a larger mass (weight) of bismuth subnitrate than of a light fluffy powder such as quinine sulfate. In addition, the amount of a particular powder that will fit into a capsule of a given size will depend on whether the powder is packed tightly or loosely into the capsule. In selecting a capsule size for a given formulation the amount of powder that represents a given dose should be weighed out and the smallest capsule size that will contain that dose should be selected. Smaller capsule sizes are preferable to facilitate swallowing. However, it is important that the capsule be large enough to hold all of the powder without the need to overfill. Otherwise, the cap might easily separate from the capsule during storage and handling. The cap is not intended to hold any powder. When filling capsules, no air space should be visible in the capsule, and powders should not be so loosely packed that they appear to be moving about within the capsule. If the amount of drug powder representing a single dose of medication (the amount to be contained in a capsule) is not sufficiently bulky to fill the capsule, then a suitable powder diluent should be added to the powder capsule formulation. Powder diluents include lactose, bentonite, calcium carbonate, mannitol, talcum, magnesium oxide, silica gel, and starch. Lactose is the most common and the most generally acceptable for extemporaneous capsule filling. The amount of filler to be added should be determined largely by trial and error.

The hard-shell gelatin capsule may be considered the dosage form of choice whenever the practicing pharmacist has to prepare a solid dosage form extemporaneously. When dealing with relatively small numbers of capsules (less than 100), it is quite feasible for the pharmacist to prepare the capsules extemporaneously. Once the powdered formulation containing the drug(s) and any diluents or other excipients has been properly prepared, the required amount of the mixture is filled into each capsule by the pharmacist, and each capsule should be checked on the pharmacy balance to ascertain that it contains the correct amount of powder. When filling capsules by hand, the powder formulation is spread out on parchment paper or on a glass slab in a smooth and fairly compact layer using a spatula. The depth of the powder layer should be less than half the length of the capsule base which is to be filled. With the cap removed, the base of the capsule is held between the thumb and forefinger and is firmly pressed or "punched" into the compact powder layer repeatedly until the base is sufficiently filled with powder. The use of finger cots may be helpful for holding the base of the capsule during the punching operation, especially if perspiration tends to be a problem. Another very helpful technique is to hold the capsule base that is being punched into the powder by placing it inside the base of another capsule, using the second capsule base as a "holder" for the one being filled. The cap is then placed on the base of the capsule that has been filled, and any excess powder which has adhered to the external walls of the capsule shell is removed by gentle tapping. The weight of the capsule is then checked, and if it contains too much or too little powder, the weight must be adjusted by removing or adding some powder as indicated; subsequently, capsules are packed either more loosely or more tightly as necessary. It is important, however, that the weight of each capsule is checked on the prescription balance. When checking capsule weight, an empty capsule of the same size should remain on the right-side pan of the balance so that the weight being determined will represent only the contents of the capsule. Rather than punching the capsules into the powder layer directly, an alternate method that is preferred by some pharmacists is to hold the capsule base in a horizontal, rather than a vertical position, and to push the powder into the capsule base using a spatula. This might be a preferable technique, particularly for powders that do not pack well, such as granular materials and salts like potassium chloride or sodium chloride.

Actually, very soluble salts such as these should probably not be administered in capsule form because the very rapid release of such highly soluble salts might cause too concentrated a solution to exist in a given site of the gastrointestinal tract and result in irritation. In addition, highly efflorescent or deliquescent powders cause problems in capsules because of their moisture-extracting effects on the hard gelatin shells.

After all of the capsules have been hand filled and the content weights checked and adjusted, the capsules should be finished by cleaning them to

remove excess powders that might still adhere to the external surface of the capsule shell. This can best be accomplished in the pharmacy setting by a gentle rolling or rubbing action of the capsules within the folds of a clean and dry towel or tissue paper.

For purposes of illustration, suppose a pharmacist has the following capsule prescription:

℞ Codeine Phosphate 20 mg
Lactose qs
Make 30 such capsules

To make 30 such capsules, the amount of codeine phosphate that would be required would be 30 × 20 = 600 mg. It should be apparent that 20 mg of codeine phosphate powder would be insufficient powder to fill even the smallest capsule size generally available. Suppose that the smallest capsule available in the pharmacy is a No. 4 capsule. By trial and error the pharmacist may determine that approximately 180 mg of lactose powder, which will be the majority component of the capsule powder formulation, would adequately fill the capsule. Allowing for the volume of 20 mg of codeine phosphate powder—180 − 20 = 160 mg of lactose per capsule—which when added to the 20 mg of codeine phosphate should fill each capsule nicely. For the total formulation then —30 × 160 = 4800 mg = 4.8 g—which is the amount of lactose required for the total formulation of 30 capsules. The pharmacist would then proceed to weigh 600 mg of codeine phosphate, 4.8 g of lactose, followed by mixing by geometric dilution. The 30 capsules would then be filled so that each capsule contains 180 mg of the powder mixture. In this particular example, the pharmacist would have to be very careful not to lose any of the powder formulation during the mixing and filling processes because codeine phosphate is a controlled substance and subject to the requirements of the Federal Drug Enforcement Administration. Every mg of such substance must be accounted for. When there are no controlled substances involved in a capsule formulation, it is general practice to prepare enough powder formulation for one or two extra capsules to allow for some loss of powder which can occur in the mixing and filling operations. Loss of powder can be minimized by carefully removing all powder from the mortar after mixing. Another advantage of preparing some additional powder beyond what is calculated as actually necessary to [illegible] desired number of capsules is that the hand filling of the last capsule is much easier. There are hand-operated capsule-filling machines which may be useful in community or hospital pharmacies where relatively large numbers of capsules are prepared routinely. Hand-operated capsule-filling machines are capable of filling up to 2000 capsules per day.

In the pharmaceutical industry, largely automated capsule-filling machines that are capable of filling hundreds of thousands of capsules per day are used. These machines separate the cap from the base of the empty capsule, fill the base, and return the cap. For capsule machines in which a very free-flowing powder is essential, and particularly machines in which capsules are filled volumetrically, a lubricant must frequently be incorporated into the powder mix. Magnesium stearate is commonly used for this purpose in concentrations of less than 1%, but other materials such as corn starch are also suitable. Because some lubricant powders are hydrophobic in nature, they can hinder the dispersion of powder in the contents of the gastrointestinal tract, thus posing a potential bioavailability problem even after the gelatin shell has disintegrated in the gastrointestinal fluids. Some capsule-filling machines used in industry operate by forming loosely compacted slugs of powder which are then transferred into the capsule. Slug formation may be aided by the inclusion of small amounts of mineral oil or microcrystalline cellulose in the powder formulation. Finishing capsules by removing excess powders that may have adhered to the shell surfaces is carried out most often by some semiautomated procedure. The process may involve rotating pans lined with oil-impregnated cloth to impart gloss to the capsules, or the pans may contain salt or other granular material to remove powder from the capsule surfaces. The use of a vacuum may also be employed for dedusting.

Two important quality control tests applied to capsule dosage forms are the weight variation test and the content uniformity test. Details of these tests will be discussed in the section on tablets because they are also applied in the evaluation of that dosage form. With the increasing importance of bioavailability and generic equivalency of solid oral dosage forms, dissolution tests, which were first applied to tablets, are now also applicable to hard-shell gelatin capsules. Included among the leading ten drugs that are prescribed generically [illegible]

gelatin capsules. They are tetracycline hydrochloride and ampicillin.

Like tablets, commercially available hard-shell gelatin capsules are used for a very wide array of drugs, and nearly every therapeutic class is represented (see USP/NF for examples). Hard-shell gelatin capsules are used commercially both for single-entity drug products and for mixtures of more than one drug. Whenever two drugs are physically or chemically incompatible in powder formulations, it is sometimes still possible to include them in a hard-shell gelatin capsule by enclosing one of the drugs in the capsule as a small pellet or tablet, or even as a smaller capsule contained in a larger one.

SOFT-SHELL GELATIN CAPSULES

Soft-shell gelatin capsules are a newer dosage form than hard-shell gelatin capsules or compressed tablets. They offer many desirable features, which accounts for their growth in popularity in recent years. The preparation and production of the soft gelatin shells, as well as the filling and sealing operations, require large-scale production technology, and the pharmacist is not involved in the preparation of this dosage form in hospital or community pharmacy practice. Nevertheless, an increasing number of important drugs are available as soft-shell gelatin capsules, and the pharmacist must have some knowledge of this unique dosage form to ensure the proper selection and use of soft-shell gelatin capsules.

As their name indicates, soft-shell gelatin capsules are more pliable and elastic than hard-shell gelatin capsules which, by comparison, are brittle. In addition, their shells are thicker. The soft shell is formed by including plasticizers and water in the shell formulation. Plasticizers used include glycerin, sorbitol, and propylene glycol. Gelatin of various types may also be chosen providing differing gel strengh. By varying the types and amounts of shell constituents, differing degrees of softness, hardness, and elasticity can be built into the capsule shell. Shell formulations usually contain antimicrobial preservatives such as sorbic acid, methylparaben, or propylparaben. They may also contain FD&C-certified colors, possibly an opacifier (usually titanium dioxide), and sometimes a volatile oil or a substance like vanillin to provide a slight, but pleasant, flavor sensation.

There are a few different mechanical processes by which soft-shell gelatin capsules may be produced and, to some extent, these various processes will determine the possible shapes and sizes of the capsules; and whether the capsules may be filled only with liquids (solutions or suspensions of drugs); or with dry powders as well. The process of the R. P. Scherer Corporation, the largest producer of soft-shell gelatin capsules, uses a rotary dye process in which large flat ribbons of shell material are formed from molten gelatin. The ribbons feed into dye rolls where accurately metered volumes of liquid-filling material are injected between the gel ribbons, forcing expansion of the pliable ribbon into the dye pockets—thus forming the capsule shape which may be oval, elliptical, or oblong. The capsule is then heat sealed, forming a seam which holds the two halves of the capsule together. If each ribbon was a different color, two-tone soft-shell gelatin capsules are formed. The capsule is then heat sealed and automatically cut out from the rest of the ribbon. The Upjohn Company and Lederle Laboratories produce soft-shell gelatin capsules by processes referred to as the "plate process" and the "Accogel process," respectively. The Accogel machine is the only one that can fill dry powders into soft-shell gelatin capsules. Once the soft-shell gelatin capsules have been formed, they are washed with a suitable solvent, subjected to a drying process, and tested for leakers.

Soft-shell gelatin capsules are most appropriate as delivery systems for liquid concentrates of drugs in an oral solid dosage form, although they can also be used as an attractive and effective means of delivering powder or granular forms of medication. Liquid solvents or dispersion media employed are vegetable oils, mineral oils, or the anhydrous water-miscible materials like propylene glycol, polyethylene glycol, glycerin, or the polysorbate surfactants. The water-miscible liquids tend to promote better bioavailability than the water-immiscible liquids. Liquids enclosed in soft-shell gelatin capsules should have a *p*H between 2.5 and 7.5 to avoid either the hydrolytic effects of strong acid on the gelatin which can result in leakage or protein precipitation or gelatin-hardening effects of strongly alkaline solutions which can cause diminished dissolution and disintegration of the capsule shells with associated bioavailability problems. Salts of strong acids and bases (sodium,

potassium, chloride, nitrate, etc.) may also react with the soft-shell material and cause problems. Emulsion systems are not suitable for inclusion in soft-shell gelatin capsules because of their high water content which may eventually leak through the shell. When suspensions of solid (powder) drugs in liquids are used as the filling material for soft-shell gelatin capsules, it is important that good suspension homogeneity be achieved, otherwise content uniformity problems will result in the finished capsule. Solids used to prepare the suspension that are encapsulated into soft-shell systems should pass through a No. 80 sieve. Of course, the use of true solution forms of medication would eliminate any potential content uniformity problems in soft-shell gelatin capsules, but sufficiently concentrated solution forms of medication cannot always be achieved due to solubility limitations, in which cases the use of suspension forms is necessary.

There are a number of considerations that account for the increasing popularity of soft-shell gelatin capsules as a dosage form for modern medications. Drugs that are liquids at room temperature, drugs that are very hygroscopic, and low-melting-point compounds that liquefy or decompose under the force of tablet compression are all examples of formulations that would be difficult to convert into two-piece hard-shell gelatin capsules or compressed tablets. Such compounds are well suited to soft-shell gelatin capsules, however. Another unique characteristic of soft-shell gelatin capsules is their brilliant and very attractive appearance which provides a rather elegant differentiation from the other common solid dosage forms (*e.g.*, compressed tablets or hard-shell gelatin capsules). While unique in appearance, the manufacturer's logo, the NDC Code, or other notations can also be imprinted on the soft-shell capsules for more specific identification. Another factor that accounts for the favorable patient acceptance of soft-shell gelatin capsules is that they are easy to swallow. When moistened by saliva, these capsules are less difficult to swallow than a tablet of even smaller size or a two-piece hard-shell capsule of comparable size. For this reason they are particularly well suited as delivery systems for relatively large doses of drugs (250 mg or more). Like two-piece hard-shell capsules, the objectionable odors and tastes of certain drugs are better masked than with uncoated tablets.

The soft-shell [illegible]

form choice that may overcome bioavailability problems encountered with certain drugs in tablet or even hard-shell capsules. The heat-seal seam of the soft gelatin shell opens to release medication into the gastrointestinal tract in less than 5 minutes after ingestion. Studies have shown that for drugs which pose bioavailability problems in tablet or hard-shell capsules, formulating them into solutions or suspensions for enclosure in soft-shell gelatin capsules may improve bioavailability considerably. The solvent or liquid dispersion medium must be chosen with care to effect the desired degree of bioavailability. Studies have shown, that for drugs with a potential for bioavailability problems (*e.g.*, digoxin), soft-shell gelatin capsules can provide greater bioavailability than elixir, solution, or commercially available compressed tablet dosage forms of the drug. In general, it appears that the soft-shell gelatin capsule offers a promising dosage form for the formulator to consider for drugs that have bioavailability problems. Both the extent of absorption and the rate of absorption can be improved by using soft-shell gelatin capsules. The favorable bioavailability characteristics associated with soft capsules is related to the liquid forms of the medication contained in the capsules as well as to the rapid disintegration and dissolution rates associated with this dosage form.

Soft-shell gelatin capsules present a useful dosage form for low-dosage drugs because they overcome the content uniformity problems encountered in such cases. Because it is a hermetically sealed dosage form, it also provides a better oxygen barrier for drugs with a high degree of sensitivity to oxidative degradation. For very costly drug entities, soft-shell gelatin capsules may be an ideal dosage form because there is negligible waste associated with production. Nevertheless, soft-shell gelatin capsules are more costly to produce than either compressed tablets or hard-shell gelatin capsules. From the manufacturer's point of view, however, they are probably less susceptible to easy duplication by generic formulators who wish to make a "look-alike" product. Although the liquid formulations contained within soft-shell gelatin capsules may contain up to 5% water, it is essential that the capsules are stored in moisture-resistant containers because exposure to moisture may result in water transfer from the atmosphere into the body of the capsule, with harmful effects to the [illegible]

tible to sticking together when stored in multiple-unit containers, and exposure to heat causes this to occur to an even greater extent. A gentle tap will usually free the capsules from one another with no harmful effects to the appearance of the capsules. Despite their sensitivity to moisture and heat, it is possible to store soft-shell gelatin capsules in appropriately designed unit-dose packaging. Soft-shell gelatin capsules with enteric release properties can be prepared by treating the capsules with formaldehyde. However, sustained-release formulations of soft-shell gelatin capsules are limited to dry-filled soft capsules rather than liquid-filled capsules.

COMPRESSED TABLETS

Compressed tablets are not only the most widely used oral dosage form, but also the most extensively used of any dosage form given by any route of administration in the United States. Although some instances of small-scale compressed tablet production using a single-punch tablet machine may exist in hospital or community pharmacy practice, the production of compressed tablets is almost exclusively the domain of the pharmaceutical industry. As the name implies, compressed tablets are formed by the application of pressure to a small portion of a powder, a granular, or a crystalline formulation confined in a small space. The tablet formulation is a mixture of materials that contain active drug(s) and various excipients which impart the appropriate flow properties, adhesiveness, and antisticking characteristics. This enables a solid dosage form to take shape and hold together once pressure is applied to the formulation using appropriate tooling and machinery.

The tooling that is fundamental to any compressed-tablet production process is a set of upper and lower punches and a die. A die is a cylindrical piece of metal, usually a special grade of steel, into which is poured the powder, granules, or crystals to be compressed. The shape and dimensions of the die determine the weight and size of the tablet by determining the volume of powder or granules that enter the die cavity. The position of the lower punch within the die during the die-filling phase of the tablet compression cycle also serves as a determining factor for volume of fill by setting the bottom of the die cavity. During the tablet compression process, the lower punch drops in the die, forming a cavity and the tablet formulation material enters the die from a feeding frame above. The punches are then forced together, applying the pressure and the tablet is formed through compression. After the tablet is formed by pressure applied by the punches within the die, the punches release the pressure as the upper punch first rises, followed by the lower punch, which then ejects the tablet from the die. The tablet ultimately formed usually has a height of approximately half the length of the depth of fill of powder in the die. The depth of powder fill in the die chamber is also related to the diameter of the tablet. For tablets of greater diameter, depth of die fill (and, as a result, the tablet height) is generally greater.

A great variety of sizes, shapes, characteristic markings, and identification codes are possible for tablets because punches and dies can be specially designed to provide for a large variety of unique tablets. Most punches are concave and produce tablets that are convex. Deeply concave punches can produce tablets that are nearly spherical in shape, resembling the shape of the old-time pills that were so popular before the widespread use of tablets and capsules. Tablets of nearly spherical shape are particularly ideal if sugar coating is to be applied after compression. Flat-face punches are also available but are less popular than concave punches. Punches and dies are precision tooling and require great care in handling. They are usually removed from the tablet press and are cleaned carefully after each production run. Damage or excessive wear can lead to misformed tablets necessitating tool replacement. Identification codes or product identification may be achieved using raised lettering on a punch face.

Tablet weights range generally from around 30 mg to well over 1 g. Tablet diameters usually range, as a function of tablet weight, from approximately 5 to 15 mm. The weight of a tablet, of course, is made up of not only the active drug(s) but also the various tablet excipients.

Tablet Characteristics

There are several important properties of tablets that are used as standards of quality control and that may, in one way or another, influence the efficacy of tablet dosage forms. These character-

istics are weight variation, tablet thickness, tablet hardness, content uniformity, disintegration, and dissolution.

Weight variation in tablets indicates a corresponding variability in total drug content for the active ingredient(s) of the tablet. The weight variation test applies to other solid dosage forms as well. Both hard and soft-shell gelatin capsules, for example, are subject to weight variation tests. Official weight variation tests, as described in the current *USP/NF*, set limits for the permissible variations in the weights of individual dosage forms, expressed in terms of the allowable deviations from the average weight of the sample. Details of the test differ somewhat for various solid dosage forms. In the weight variation test for tablets, 20 tablets are weighed individually and the average weight is calculated. The weights of not more than two of the tablets may differ from the specified percentage difference tolerance applicable to that tablet, and no tablet may differ by more than double that percentage. The percentage difference weight variation tolerance is 10% for tablets which weigh 130 mg or less, 7.5% for tablets that weigh from 130 to 324 mg, and 5% for tablets that weigh more than 324 mg. The "weight" that is referred to in the weight variation test is, of course, the total weight of the tablet, not just the labeled potency (*i.e.*, the weight of the active drug component). Coated tablets are exempt from the requirements of the weight variation test because greater variations in the weight contributed by the coating itself are to be expected. Weight variation tests are particularly valuable as in-process control tests, since changes in tablet machine settings can be quickly detected and appropriate alterations can then be made to correct the weight of the tablets being produced. Persistent weight variation problems may result from a poor tablet powder or granule formulation with inadequate flow properties, too large or too small a granule size; inadequate lubrication causing the powder or tablet pieces to stick to faces of the punches or walls of the die; or a malfunctioning tablet press.

Tablet thickness and tablet diameter constitute the dimensions of the tablet. The tablet thickness may vary when tablets are of variable weights, but variation in tablet thickness may also occur even when tablet weights remain constant. Whenever the latter situation prevails, it is usually caused either by variations in tablet hardness that result from improper feeding of the granules into the die cavity, or by variations in the machine settings. Tablet thickness is usually measured during tablet production runs to serve as an in-process control. Excess variation in tablet thickness can lead to problems in packaging and may also cause automatic counting devices to malfunction.

Tablet hardness is a property of tablets that may be measured by using several commercially available devices designed specifically for that purpose. These mechanical testers for tablet hardness vary in appearance and to some extent in their principle of operation. The Pfizer hand-operated tablet-hardness tester and the Strong-Cobb hardness tester are examples of devices that are used to measure tablet hardness. The Pfizer device is somewhat similar to a pair of pliers. Pressure is applied by a hand grip and the force required to break the tablet is measured in pounds or kilograms on a dial. When hardness is used as an in-process control, or as a research and development tool, it is essential that all readings are taken on the same type of instrument. Although all tablet-hardness devices essentially measure resistance to crushing, the readings from one type of device to another are not directly correlated. Adequate hardness is related to the ability of a tablet to withstand cracking, chipping, or breaking apart during normal handling and shipping. In recent years it has also been recognized that tablet hardness is related to the disintegration and dissolution capabilities of tablets. Therefore, it is an important factor in bioavailability considerations.

Content-uniformity tests are especially important in tablets in which the active ingredient(s) make up a relatively small fraction of the total tablet weight. This is because content-uniformity tests measure how thoroughly and homogeneously the drug(s) are distributed through the tablet. Problems might arise from inadequate mixing or granulation techniques when preparing the materials for tabletting. The USP/NF generally specifies a content-uniformity test for tablets with a low fraction of active ingredients and also for sugar-coated tablets. The test is performed on a sample of 30 tablets. Any 10 of the 30 are assayed individually to measure the potency of the active ingredient. The requirement of the content-uniformity test for tablets is met if each of the ten tablets falls within 85 to

115% of the average limits specified in the official potency assay (generally performed on a larger sample of tablets rather than on individual tablets). If not more than one tablet falls outside that range, the content-uniformity test requirement may still be met, provided that none falls outside the range of 75 to 125%, and that the remaining 20 tablets, upon individual assay, are each within the 85 to 115% range. Content uniformity is a test that also may be applied to other dosage forms, particularly capsules.

Dissolution tests and disintegration tests (which were forerunners of dissolution tests) are among the most significant compendial tests for tablets. Dissolution tests are generally acknowledged to be the best *in vitro* test indicator for bioavailability. Dissolution tests are extremely useful in the formulation and process design steps of tablet development. Dissolution tests are also important compendial quality control standards. Although dissolution tests have, to a large extent, made disintegration tests superfluous, disintegration tests still find some use and are still employed as a pharmacopeial test. Like several of the other tests applied to tablets, disintegration and dissolution tests are not limited to tablets but are also applicable to capsules. The disintegration test is not applicable to all tablets. For example, it would obviously not be intended for chewable tablets. Disintegration of a solid dosage form is achieved when all the particles of a dosage unit have passed through the screen, or when any residue of the unit, except fragments of insoluble coatings or capsule shells, remaining on the screen of the test apparatus exists as a soft mass having no palpably firm core. For details on current compendial standards and procedures for disintegration and dissolution testing, see these sections in USP/NF.

Ingredients of Tablet Formulations

In addition to the active ingredients, compressed tablet dosage forms also contain various types of excipients. In fact, compressed tablets generally contain a greater number of excipients than most other dosage forms. As with other dosage forms, tablets may contain coloring agents. Chewable tablets also contain sweetening agents and flavors. The excipients that are somewhat unique to compressed tablets are *diluents*, *binders*, *disintegrating agents*, and *lubricants*.

Tablet diluents, also referred to as *fillers* or *bases*, are used mainly to serve as vehicles for the drug and to increase the bulk of the tablet, a particularly important function when dealing with very potent low-dose drugs. The traditional materials that are used as tablet fillers are as follows:

1. *Calcium Carbonate*
2. *Calcium Phosphate, Dibasic*
3. *Calcium Sulfate, Dibasic*
4. *Dextrose*
5. *Kaolin*
6. *Lactose*
7. *Mannitol*
8. *Microcrystalline Cellulose*
9. *Sodium Bicarbonate*
10. *Sorbitol*
11. *Starch*
12. *Sucrose*

These diluents make up from as little as 5% to as much as 80% of the total weight of the tablet. Fillers such as calcium carbonate, calcium phosphate, and starch usually do not exceed 20% of the weight of the tablet, whereas fillers such as lactose, sodium bicarbonate, microcrystalline cellulose, and sucrose may exceed 50% of the formulation weight. Calcium carbonate, calcium phosphate, kaolin, starch, and cellulose are insoluble fillers, while the others are water-soluble. Several new, partially hydrolyzed starches are now available as "soluble" starch. These fillers may be used with either the wet granulation method of tablet production or the slugging method, which is also referred to as *dry granulation*. Lactose in spray-dried form, anhydrous lactose, calcium phosphate dibasic, crystalline sorbitol and mannitol, and microcrystalline cellulose are directly compressible, and are particularly useful in the newer direct compression method of tablet production. Crystalline drug is mixed with the diluent and directly compressed into finished tablets by this technique.

Some of the diluent materials have abrasive properties, meaning that they cause wear on the tablet machine tooling. Frequently, tablet excipients perform more than a single function. For example, dextrose, lactose, sucrose, sorbitol, and mannitol exhibit some binder properties. Starch and microcrystalline cellulose can serve both as binders and disintegrants, depending on how they are used and incorporated. Lactose and sucrose impart hardness to tablets, while starch, kaolin,

and dextrose add softness. Sometimes these diluents also function as absorbents, absorbing moisture or oil, thus facilitating tablet processing.

Disintegrants or disintegrators are another type of essential excipient in the preparation of compressed tablets, and are also referred to as *disruptors* or *solubilizers*. Such disintegrating agents are needed in order to cause a tablet to rupture or break apart when it comes in contact with the aqueous fluids of the gastrointestinal tract, thus exposing more surface to the fluids and hastening disintegration, dispersion, and the dissolution processes. Disintegrating agents have been recognized as especially important components in compressed tablet formulation, with the increasing interest in bioavailability that arose throughout the 1970s. The mechanisms of action by which such agents function are not fully understood, but they are thought to involve swelling, porosity, and capillary action. Cornstarch has traditionally been the most widely used tablet disintegrant, and is still regarded as the best agent for disintegration-imparting properties in many formulations. When used as a tablet disintegrator, the starch is added at 2% to 20% of the formulation by weight, with 5% to 10% being common concentrations. To function as a disintegrator, starch should be added as a dry powder to the final formulation, or as a dry powder to the original mix for either dry or wet granulation. A combination of both these approaches may also be employed. Starch in paste form is used as a binding agent, but addition of starch in this form will not usually provide an effective means of imparting disintegration properties to tablet formulations.

Other disintegrators besides starch are microcrystalline cellulose, carboxymethylcellulose, methylcellulose, veegum, alginates, agar, bentonite, certain surfactants, and certain ion exchange resins. The inclusion of agents that cause a tablet to undergo effervescence upon contact with water can also serve to ensure tablet disintegration. Combinations of sodium bicarbonate and citric acid will accomplish this. However, such tablets are moisture sensitive, which limits this approach. The disintegration characteristics of a tablet are not solely a function of the properties of the disintegrator, but depend on other factors such as the binding agent, the lubricating agent, and other features of the processes involved in tablet compression that influence tablet hardness.

Binders or granulators are agents that are used to impart cohesiveness to the powdered tablet formulation, thus allowing the powders to be formed into granules that have a consistency that promotes suitable flow during the tableting processes. Sufficient binding agent is necessary to maintain the tablet intact after compression and during normal storage shelf life, dispensing, and usage by the patient, but an excessive amount of binder may cause excessive granule and tablet hardness, with slow tablet disintegration and dissolution, and inordinate wear and tear on tablet press tooling.

Acacia, glucose, and sucrose are relatively strong binders; agar and starch paste are relatively weak; and dextrose, gelatin and lactose are of intermediate strength. Binders can make up as little as 1% or as much as 20% of the dry weight of the tablet formulation depending on the strength of the binder and the degree of binding desired. Binders are usually water-soluble materials, and they are most often added in the form of a solution for incorporation with the powders of the tablet formulation, to form a damp, granular (but not pasty) mass. The solutions are made up to contain from 5% to 50% binder by weight, and sometimes flavoring and coloring agents are included in the binder solution. There are also procedures whereby binders may be incorporated in the form of dry powders.

Lubricants may provide glidant effects by coating and lubricating particle surfaces, thereby serving to improve the flow properties of tablet granulations. They may provide antiadhesive qualities to prevent adhesion of materials to punches and dies during the tablet compression cycle. They act as lubricants between the walls of the die cavities and the tablet surface to facilitate tablet ejection from the dies. Calcium or magnesium stearate, stearic acid, and talc are the best and most commonly used lubricants. In addition to these insoluble lubricants, there are also some lubricants that are water-soluble, at least to some extent. These include starch, sodium stearate, and the solid high molecular weight polyethylene glycols (carbowaxes). Lubricants generally comprise from 0.25% to 5% of the total tablet formulation depending on the agent selected. Lubricants are usually added to the tablet granulation as a finely divided (60 mesh to 200 mesh) powder. Gentle tumbling in a mechanical blender serves to incorporate the lubricant into the granulation. Combinations of more than one lubricant are sometimes employed, and a small

amount of a disintegrant may also be combined with insoluble lubricants to reduce their retardant effect on dissolution.

Preparing Tablet Formulations for Compression. The most widely used approach to preparing the ingredients of a formulation for tablet compression is the wet granulation method. The overall objective of wet granulation is to provide a granular consistency in the product that is to be compressed, with resultant suitable flow and compressibility properties. Powders generally flow poorly and do not compress well. The powdered ingredients of the drug, the diluent(s), and the disintegrator are sieved and mixed, and then the granulating liquid, usually the binder solution, is incorporated to provide a slightly moist doughy mass. The damp mass is then screened, usually through a 6 mesh or 8 mesh screen, to form the wet granulation. The degree of moisture of the wet granulation must be very carefully controlled. If the mass of moistened granulation is too wet, granule formation will not occur properly and the dried granules will become too hard, with resultant compression problems and mottling of the tablets. If they are not moist enough, the granules will be too soft and break apart before compression occurs.

After the wet granulation is formed either by passing the slightly moistened mass through a screen by hand or with the use of a mechanical granulator, the granules are placed on large sheets of paper on shallow trays. These trays may be placed in drying ovens that have a circulating air current and thermostatic temperature control of the oven or air. The drying of the granules is an important step in the production of tablets because an excessive residual moisture content can influence drug stability, tablet appearance, and the ability of the dried granules to undergo proper compression. Therefore, the drying time, temperature, and extent of air flow must all be carefully regulated. Fluid bed drying is a more modern approach than the traditional tray drying. It is more rapid than tray drying, avoids color migration when dyes are included in the formulation, produces more uniform drying of the total formulation, and eliminates the caking of granulation on trays. In the fluid bed drying process, granules are actually dried by suspending them on a stream of warmed, filtered air.

Once drying is completed, the dried granules are reduced to a more uniform particle size, usually by mechanical screening. The specific particle size range to which the dried granules are reduced depends upon the size of the tablet being prepared. For very large tablets (over 12 mm), an 8 mesh or 12 mesh screen may be used, while for smaller tablets, sieves of 14 mesh to 20 mesh are employed.

Presently, there is an increasing trend toward the use of dry methods of readying tablet formulations for compression. These approaches may be simpler than the wet granulation method and may improve certain characteristics of the tablet. Drugs that are moisture-sensitive, for example, might be better tableted by means of a dry method. The use of certain diluents such as spray-dried lactose, crystalline or granular sorbitol and mannitol, microcrystalline cellulose (Avicel), and other direct compression materials have, since the 1960s, resulted in an ever increasing application of direct compression as a technique for preparing tablets in the pharmaceutical industry. Slugging (also termed double compression), is another and older technique that may be employed as a dry method for tableting. In this method, the powders of a tablet formulation are precompacted into "slugs," or semi-compacted masses, by feeding the powders into a heavy-duty compacting machine. These "slugs" are then screened to produce granules of appropriate size prior to tableting. Such double compression may result in dense, hard tablets with longer disintegration and dissolution times than is possible with the other two techniques.

Tablet Manufacturing Processes. Once the powders that go into a tablet formulation have been properly prepared for tableting, they are fed into a tablet compressor (see Fig. 7–3) through a feeding device or a "hopper," fed into the die (usually by gravity feed), compressed into a tablet within the die by the action of an upper and lower punch, and finally the finished tablet is ejected. The punches and dies must be selected based on the type of tablet press being used, the size and shape of tablets to be prepared, and the particular lettering or design to be inscribed on the face of the tablet. The tablet press must be set up in a way that ensures that the tablets produced will have the appropriate content uniformity, physical stability, and preselected weight. Weight variation and tablet hardness, as well as other tablet characteristics may be moni-

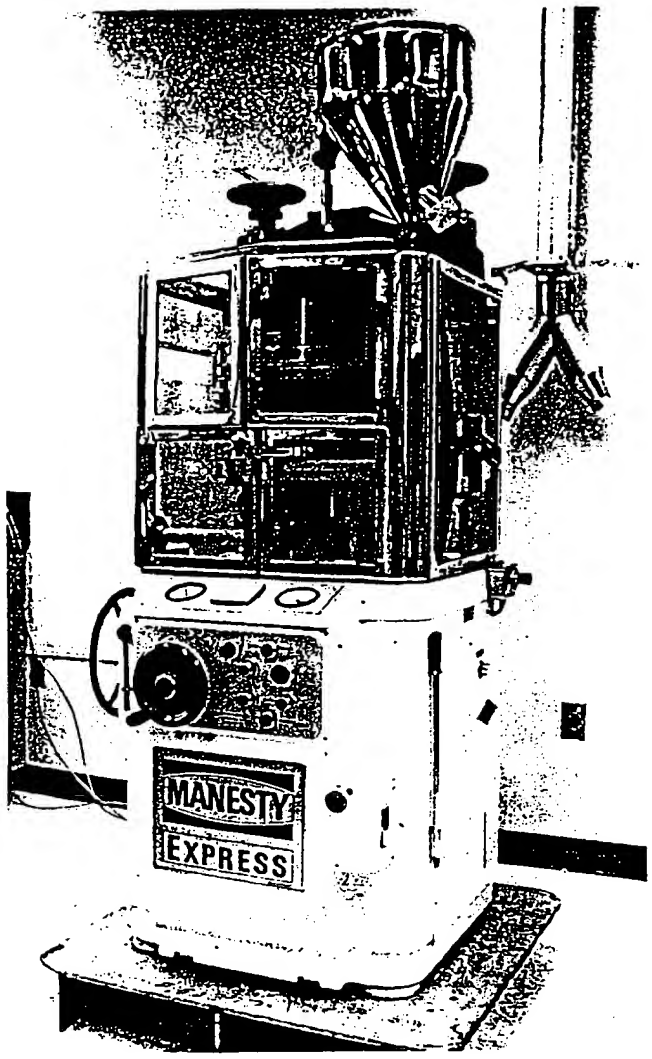

Figure 7–3. The Manesty Express is an example of a modern high speed rotary tablet press. (Courtesy of Squibb)

tored throughout the production cycle as in-process controls. Although the tablet machine is carefully adjusted to produce tablets of appropriate weight, hardness, and other characteristics at the start of a production run, it may be necessary to make further adjustments based on the results of the various in-process controls as the cycle of operations proceeds. Modern tablet machines allow for varying degrees of automated control, including controlled force-feeding of the granulation from the hopper into the die, continuous monitoring of the compression force, and thereby, continuous monitoring and automatic control of tablet weight.

There are basically two types of tablet compressors, single punch tablet machines and rotary presses. Single punch machines cannot produce tablets as rapidly as rotary machines, and therefore, single punch units are useful only in the preparation

of smaller production runs. Single punch machines are available as hand-operated models, but the majority of them are motor driven. Rotary machines, instead of having a fixed die plate like the single punch machines, employ a revolving head (turret) carrying several sets of die stations. As the head containing the various punches and dies rotates under the feed frame, each die becomes filled. Subsequently, the revolving head carries the filled die station between two rollers that apply gradual pressure to the upper and lower punches. The resulting pressure that produces the tablet is somewhat more gradual than the sudden, swift stroke of pressure that results from the use of single punch tablet machines. This more gradual application of pressure may eliminate some possible problems that result from air entrapment during the compression cycle. The production capacity of rotary tablet machines may be increased by increasing the rate of rotation of the turret and by increasing the number of filling stations. Machines now exist that can produce up to 10,000 tablets per minute.

One of the problems that can occur in tableting is *capping*, which refers to the top of the tablet cracking and splitting off as a thin layer or cap. It is thought to be related to air entrapment during compression, and is more common with biconvex tablets. More extensive problems related to capping may result in the "explosion" of tablets upon ejection from the tablet press. Sticking and filming are also problems that can become evident during the tableting cycle and, like capping, may be related to improper choice of excipients, incomplete dryness, worn punches and dies, or excessive compression pressure. Sticking involves tablets not ejecting cleanly from the lower punch, resulting in imperfections on the face of the tablet. Filming is a form of sticking in which a film of powder builds up on the punch face so that the tablets that are produced appear misformed and rough. Pharmacists will occasionally see such defective tablets in commerce. They should be returned to the supplier or manufacturer.

Tablet machines and the associated tablet tooling are rather complex and require great care in use and operation. It is also essential that they be meticulously and completely cleaned between runs to ensure that no cross contamination occurs from one batch of drug to another.

The great majority of tablets that are used today are compressed tablets, but preparation of tablets by molding provides another approach to the preparation of small tablets. Molded tablets are prepared by forcing dampened powders into die cavitites of a mold board, by hand, using relatively modest pressure. Solidification occurs as the dampened mass dries, with the formation of cohesive crystal bridges, and the tablets are subsequently ejected from the mold, usually by using a matching peg board, with mild pressure. Such tablets are not nearly as hard as compressed tablets and are used when small soluble tablets are needed. Lactose and powdered sucrose in various proportions usually make up the tablet base, and such small tablets are useful only in cases in which small quantities of drugs need to be incorporated into the tablet. Sublingual tablets of nitroglycerin, for example, might be candidates for preparation by molding. In preparing molded tablets, the moistening of the powders is brought about with hydroalcoholic solutions, the major component of which is alcohol. Molded tablets are much more friable than compressed tablets, and greater abrasion occurs with them. Small tablets of this type are often referred to as *tablet triturates*. They may also be prepared by compression techniques, and this approach reduces the friability and certain other physical instability problems.

Chewable tablets represent another specialized category of tablets. They are sweetened, flavored and often colored, and they provide the convenience of a solid unit dosage form for patients who cannot swallow a tablet or capsule. Mannitol usually serves as the base of chewable tablets, and it provides a cool, sweet sensation as it dissolves. Many children's vitamin products are available as chewable tablets.

CONTROLLED-RELEASE DOSAGE FORMS

For most drugs the intensity of the pharmacological effect at any time is related to the amount of active drug in the individual's system following absorption. This amount of drug at any given time is the result of the pharmacokinetic properties of the drug—a balance between absorption, distribution and elimination (as explained in Chapter 4). If a drug is to be used over a long period of time, it is often desirable to achieve and maintain a suitable

This is Exhibit H referred to in the Declaration of Dr. Michael M. Lipp, sworn this 12th day of November, 2003

A Commissioner, Notary Public
for taking oaths

CINDY A. SRAGG
Notary Public
My Commission Expires
January 23, 2009